Comparative Anatomy, Pathology and Roentgenology of the Breast

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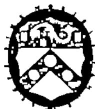
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The following illustrations have appeared in previous publications by the authors and their associates

The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Figs 141, 142, 154, 155, 156, 174, 183 and 189

The A M A Archives of Surgery, Fig 188

Annals of Surgery, Fig 157

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The British Journal of Radiology, Fig. 151.

The Bulletin of the International Association of Medical Museums, Figs 20 and 21

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Introduction

Sir Astley Cooper in *The Anatomy and Diseases of the Breast* says "I have restricted myself to describing from my own preparations only, and if every author in our profession would adopt this plan and merely write on what he is capable of demonstrating, preserving and exhibiting to others, the medical world would not be overwhelmed with those crude opinions, theories, and conjectures, which, according to the present system of quoting all that has been written, are sure to compose the greater part of the works that issue from the press My rule has been to publish that only which I could show to those who were skeptical, and were yet desirous of arriving at the truth."

No apologies are needed for imitating so eminent an example. Indeed, to do justice to all that has been written on the human mammary gland would fill several volumes We have endeavored to confine our writing to matters of which we have personal knowledge and have for the most part worked out for ourselves The application of two hitherto little used technics, the slicer method for cutting whole breast sections and above all the roentgenographic experience of Gershon-Cohen have enabled us to investigate the mammary gland from a new angle. We have made use of the work of others only in so far as was expedient as a background or a corollary to what we ourselves have observed To compensate for our apparent neglect, we append a full bibliography hoping thereby that all important papers will be consulted by those who are interested.

No work stands alone. We are indebted to many who preceded us and to many who cooperated and worked with us Of those who have gone before, the pathologist would name Professor Frederic Wood Jones and Sir Lenthal Cheatle, whose teachings were a lifelong inspiration. Of our contemporaries we can single out only one, Dr Raoul Leborgne. We owe much to his persistence in

applying roentgenographic technics to the examination of the breast, as well as to his generosity in passing on his knowledge.

Our particular thanks are due to Lolita Moore, our able and indefatigable assistant, for her help in looking up and sifting literature in all languages, indexing and tabulating cases, and for many suggestions for perfecting technic.

It is a pleasure to acknowledge the warm and sympathetic co-operation of the surgeons and physicians of our staff Our particular thanks are due Dr. Henry Brody and Dr. Irving Young of the pathological staff for their many kindnesses during the progress of this work.

The original investigations on the pathology of the breast were begun many years ago, thanks to the facilities afforded by the laboratories of the Woman's Medical College and to the generosity of Mrs Beatrice Fox Griffith and Dr. Corinne Trullinger Chamberlin

In recent years through the generosity of Dr. J. C. Doane, former Medical Director of the Albert Einstein Medical Center and Chief of Medical Services, now Professor of Clinical Medicine at Temple University, a fund created by Mrs Frank Strick was made available for a survey of breast disease in asymptomatic women. The continuity of the work has now been assured by a research grant from the National Institutes of Health.

We also wish to thank the editors and authors for permission to reproduce Professor Engel's illustrations from the *British Journal of Childhood Diseases*, and Dr. J Grynfellt's diagram from the *Archives d'Anatomie Microscopique* Dr J C Valentine generously provided the photos for Figs. 1 to 3, and Dr. Jacob A. Vastine for Fig 69

General Remarks Evolution of Roentgenology of the Breast

THE FIRST attempt to diagnose mammary disorders by means of the x-ray film was made by Salomon in 1913 Salomon took x-ray films of surgical specimens and compared the clinical, radiological, and pathological findings in carcinoma of the breast. The outbreak of World War I put a stop to these efforts, and the subject was not revived until 1930 In that year S L. Warren published a roentgenologic study of the breast. Seabold in 1931 described radiologic changes during the menstrual cycle and gave criteria for the differentiation of normal from abnormal conditions in the breast. He succeeded in measuring fibroadenomas roentgenographically and demonstrated alterations in the size of the tumors Lockwood and Stewart (1932) studied the menstrual cycle roentgenographically and distinguished between Cheatle's mazoplasia and "cystiphorous desquamative epithelial hyperplasia" on the film. Ries (1930) showed that it was unsafe to inject iodized poppyseed oil or foreign material into a duct, as abscesses would result. Mammography was later perfected by Leborgne (1953) From 1935 onward pneumography of the breast was attempted but no great advance was made along this line. Injection of thorotrast was popular until it was discovered that tumors might follow its use (fig. 189)

The more recent work of Gershon-Cohen shows that artificial aids are unnecessary in the diagnosis of breast lesions In the period from 1937 to 1948 he made notable progress in accurate diagnosis of malignant tumors Without minimizing the difficulties encountered in the interpretation of abnormal roentgen mammary patterns, he tirelessly advocated the use of roentgenograms as an aid to clinical diagnosis and was the first to demonstrate the feasibility of detecting occult carcinomas (1948) At the same time many workers were discouraged by the uncertainty of their

results. Two factors hampered progress—unsatisfactory technic and lack of exact pathologic knowledge.

Leborgne, working in Montevideo, was the first to propose a technic which, while contradicting many of the established rules, achieved a degree of visualization of breast structures hitherto considered impossible His methods have gone far toward making roentgenography of the breast an exact science

Very thorough knowledge of breast pathology is a *sine qua non* for interpretation of breast films. The older radiologists who followed Cheatle were able to diagnose mazoplasia fibrosa from cystiphorous desquamative hyperplasia and to distinguish both from carcinoma. But this could only be accomplished when the lesions were well developed. Since Cheatle, breast pathology has become more and more confused Terminology is inexact and extremely variable. Classification depends chiefly on the views of the pathologist or surgeon. Many writers content themselves with such expressions as fibrocystic disease, cystic mastitis, mastopathy and even the long outdated chronic mastitis. They seldom define what they mean and do not distinguish one form of dysplasia from another. In this inchoate welter the unfortunate radiologist drifts on a sea of confusion To make matters worse, few pathologists have studied entire breasts Detailed examination of histologic sections is essential to complete diagnosis, but does not help the radiologist who must look at the organ as a whole, compare it with its fellow, and draw his conclusions therefrom.

The authors realized that progress in x-ray diagnosis could only be made by careful comparison of the film with the actual specimen. The method followed was to make whole serial sections of the frozen breast, stain the series, and examine the tissue under the dissecting microscope The sections were then set up alongside the x-ray film. Each was compared with the other The counterpart of opacities discerned on the film was studied in the section; structures seen in the section were studied on the film. After the first hundred patients were examined it was obvious that the cases fell into certain categories. Furthermore the x-ray films and

sections matched clinical groups as revealed by the records Classification might almost be said to have made itself

The question has been asked "Why should we burden ourselves with the problems of x-ray examination of the female breast? A biopsy is usually necessary and will give the diagnosis anyway' In the words of Kremens (1958), one may reply that " there are no short cuts in medicine Any diagnostic information which may be obtained by additional study without detriment to the patient, should be sought without stint or reservation There is no thought of omitting roentgen study of the chest in an individual with hemoptysis and a positive sputum! There similarly should be no hesitation to obtain whatever additional information may be made available by a roentgen breast examination despite the clarity of the clinical picture. Completely unsuspected pathology may be uncovered either in the breast under observation or, as has occurred in many instances in our experience, in the contralateral breast One of the greatest values of the roentgen ray has been the opportunity it has afforded in detecting a disease process *before* it is clinically manifest"

Indications for mammary roentgenography fall into two categories

(a) x ray examination is necessary for detection and localization of a malignant tumor, and
(b) it affords a tool for the follow-up of patients or for scientific observations

The first group comprises cases of suspected and unsuspected cancers Definite diagnosis cannot be made clinically and in these patients x-ray examination is mandatory

Suspected but nonpalpable cancers are usually of the type known as occult. An occult cancer in the strict sense is one in which discovery of some remote symptom or sign, such as localized pain over the spine or an enlarged axillary node, leads to the suspicion of breast cancer, but no mass is felt. A nonpalpable breast cancer can only be located by means of the x-ray film. The

fact that a tumor is suspected or even known to be present greatly facilitates the radiologist's task. A needle in a haystack may be hard to find, but in the absence of certainty as to the needle's existence, the search would seem hopeless. Whatever the explanation, occult carcinomas are among the most easily diagnosed of the nonpalpable tumors.

Unsuspected neoplasms until very recently lived up to their name. But with help of the x-ray film a number of them have been debunked. The three principal ways for a cancer to escape detection are: 1. The malignant tumor is felt but wrongly diagnosed benign. 2. It is masked by other lesions. 3. The growth is too small for palpation.

In matters of mistaken diagnosis, a tumor is felt, but it is so circumscribed and movable that suspicion of its malignant nature may not be entertained. For example, a duct carcinoma, even when it has reached extensive proportions, is frequently mistaken for a benign tumor. Biopsy is likely to be postponed. The x-ray in these cases gives an unequivocal answer. A reluctant patient is more willing to submit to operation and valuable time may be saved. Another reason for mandatory x-ray examination of all benign lesions is that while the diagnosis of the palpable lesion may be correct, a small preclinical carcinoma may be present in another part of the breast. Too often the patient is lulled into a false sense of security by the removal of a cyst or other benign lesion when the real culprit lies latent to appear perhaps years later when it is no longer curable.

X-ray examination is likewise indicated in all cases of nodularity or "lumpiness" of one or both breasts whether a dominant mass is present or not. These cases are very common. In most of them adenosis is the underlying or masking lesion. In some patients the adenosis has passed on to hyperplastic fibrosis In a few, mazoplasia cystica has developed on the basis of adenosis. Rarely, the nodularity is due to multiple fibroadenomas In the great majority of cases of lumpy breasts the condition is benign and remains so, but should a carcinoma develop it is not likely to be discovered for

a very long time. Often the growth is away from the region of the lump and it is not uncommon for multiple operations to be performed on these women without discovery of the cancer Hence the necessity of roentgenography as a preliminary to biopsy

All women presenting vague, unusual, or unaccountable symptoms referred to the breast must be examined roentgenographically Pain is sometimes the presenting symptom of a nonpalpable carcinoma Indefinite thickening in any part of the breast should likewise come under suspicion Finally, x-ray examination gives reassurance to a normal patient with cancerophobia and a positive family history of breast cancer

Carcinomas remain asymptomatic for a very long time. X-ray examination leads to the detection of a tumor long before it can be recognized clinically Studies of rate of growth of cancers have recently enabled us to form some estimate of their duration. The preclinical diagnosis of mammary carcinoma gives a much greater hope of surgical removal before metastases have occurred than would have been previously considered possible. For this reason roentgenography of the breast should form part of any program for periodic health examination of women.

In the second category, x-ray studies, while not mandatory, have proved their worth in a number of ways They are helpful in the postoperative follow-up of patients and even more so for evaluation of therapy when operation is not contemplated Considerable increase in knowledge of breast pathology has resulted from studies of normal breasts and of benign lesions Study of precancerous lesions and their recognition by means of x-rays affords reason to hope that in future many lesions will be treated in the precancerous stage and mutilating operations avoided.

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PART I

The Normal Breast

The Normal Breast

THE INFANT BREAST

A DETAILED description of the embryology of the breast is not within the scope of this work. The milk line, appearing at six weeks' intrauterine development, the budding of the epithelial cells, and the postnatal enlargement of the organ are well known. The secretion of "witch's milk" deserves more attention than is usually accorded it. Grynfeltt (1937) gave an admirable description of the infant breast and its secretions Recently J C. Valentine has amplified our knowledge and added new facts which throw considerable light on the vagaries of the mammary gland in later years His observations await publication.

In all fetuses of seven months' development or upward that survive three or four days after birth, the ducts are dilated and filled with a fluid which is similar to adult colostrum and is secreted in the same way This may be discharged as "witch's milk" The condition usually disappears in a few days, but should it continue, true lactation acini are formed. In some cases the secretory changes parallel those of secretory disease in adults (figs 1, 2, 3) In one of Valentine's infants, changes suggestive of plasma cell mastitis, a complication of secretory disease in adults, were found Even in these cases, postnatal mammary development seldom persists beyond six months of age. After six months, childhood enlargements are no longer physiologic. They must be classified with the pathologic hypertrophies Rarely, postnatal hyperplasia persists beyond infancy, or regresses to return again.

Secretion in the newborn is probably due to the same hormones that induce secretion of colostrum in the mother Persistence of lactation after the first few days is more difficult to explain. The small follicular cysts of infants ovaries cannot be invoked, for males are equally affected, nor does it follow that the mother's milk is to blame, since many of the babies are bottle fed



Fig. 1 Infant breast at term. The ducts are dilated and lined by proliferating secretory cells which are discharged into the lumen. Acini are seen here and there between the ducts

THE ADOLESCENT BREAST

to three years before the menarche, the female breast enlarges rapidly In the male there is hyperplasia, but it is slight. The female gland soon outstrips its capsule to push in various directions into the surrounding tissue. The ducts, with their sheaths, subdivide and penetrate farther and farther, compressing the fat lobules so that at the menarche, except in obese subjects, fibrous tissue predominates and only occasional islands of fat are seen. In many breasts at this age, fat has completely disappeared

Fundamentally the process is similar in all girls, but very wide variations are seen in rate and degree of development. A comparison of adolescent breasts by means of serial whole sections shows no exact correlation between age and development.

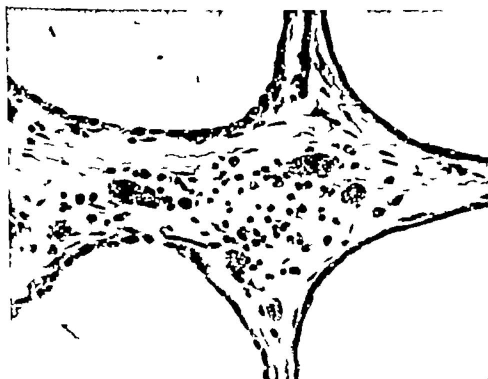


FIG 2. Infant breast. Cystic dilatation of duct following involution of the secretory phase. (Type IV of Valentine's classification.) Female aged four months not breast fed Death from bronchopneumonia. (Courtesy of Dr J C. Valentine.)



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THE ADOLESCENT BREAST

From six months to the onset of puberty the breast ducts lengthen and divide, but the process is a very slow one and the organ does not keep pace with body growth This is perhaps the only period in which the breast may be said to be "resting".

Up to the onset of puberty there is, as far as we know, no essential difference between the male and female breast, but two

to three years before the menarche, the female breast enlarges rapidly In the male there is hyperplasia, but it is slight The female gland soon outstrips its capsule to push in various directions into the surrounding tissue. The ducts, with their sheaths, subdivide and penetrate farther and farther, compressing the fat lobules so that at the menarche, except in obese subjects, fibrous tissue predominates and only occasional islands of fat are seen. In many breasts at this age, fat has completely disappeared

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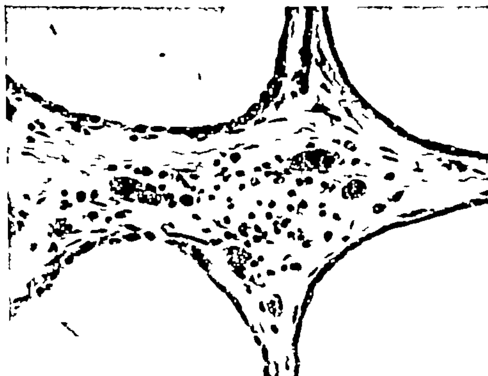


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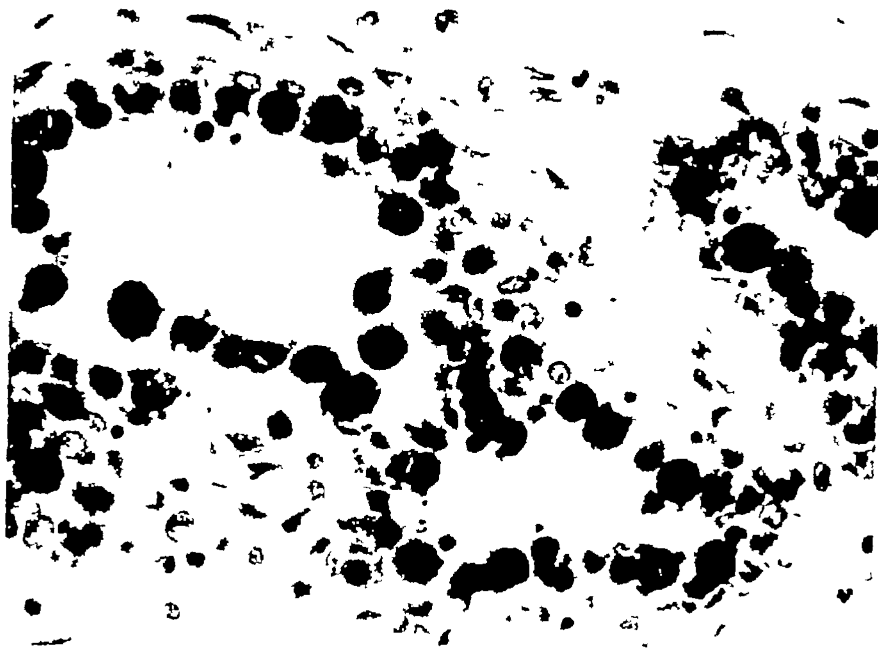


FIG. 3. Infant breast. Osmic acid preparation to show secretion of fat in the lining epithelium of the acini. Eight months fetus. (Courtesy of Dr J. C. Valentine.)

The adolescent breast before ovulation consists only of ducts (figs. 4, 5, 6). There are no lobules. The ducts branch along their whole course from the nipple to the pectoral fascia. In the tissues seen under the dissecting microscope the first thing that attracts attention is the club-shaped swelling of the majority of the terminal ducts (fig. 6B). A few of the growing ducts are round—this is mostly an earlier stage—and not infrequently, where a duct is about to bifurcate, a kidney-shaped structure is seen. Under the dissecting microscope these formations resemble bunches of cysts (figs 6c and 101).

In the adolescent breast prominent spurs or ridges are seen in the long axis in practically all ducts, although not usually in the end bulbs (figs. 6B and 6D) The ridges are elevations projecting into the lumen of the duct They consist of the usual two layers of

FIG 4. Breast of a ten year-old girl. Anesthetic death An early stage of adolescent development is shown. Note primitive budding and cystlike dilatation of ducts. Growing points in the duct wall produce outpouchings separated by broad indentations Paraffin section.

FIG 5 Normal adolescent breast from a girl aged twelve years Before menarche. Slicer section.



. 6 A



B

epithelium and the intraductal connective tissue They are as much a part of the wall of a normal duct as are the intervening grooves At first glance they might be thought to be due to folding of the



C

FIG 6 Normal adolescent breast from a girl aged thirteen years Death from rheumatic pneumonitis two days after onset of acute illness She had never menstruated.

A. Slicer section through entire breast The development is not uniform, a" shows area of more advanced subdivision of ducts.

B Slicer section magnified to show swelling of terminal portions of developing ducts

C. Detail of developing ducts, note resemblance to cysts



D



FIG. 6 E

D. Ducts are cut transversely. They show ridges projecting into the lumen.
E. Photomicrograph to show the earliest stage of duct formation. Paraffin section × 1000.

wall of a duct following shrinkage from emptying of its contents But observations made on large numbers of sections show that when ridges are traced through to their final destination they eventually meet to form the proximal boundary of the mouth of a new duct. The significance of the ridges is made clear by a study of the way in which ducts are formed The first change is a proliferation of epithelial cells in the wall of a duct (fig 6E) If this proliferation were uniform, all that would happen would be that the duct would become larger and longer But as the illustration shows, the process is not uniform The cells proliferate at certain points and grow outward. At first they are seen as a simple clump of cells Very early a rudimentary lumen appears The intervening wall which has not proliferated is left behind and becomes a ridge projecting into the lumen (fig 6D) This description is based on paraffin sections and does not give a clear idea of the whole process Seen tridimensionally in slicer sections, the budding ducts look like a toy balloon on a thick stalk. Later a broad indentation appears in the end bulbs (fig 4), and indicates further subdivision. While the most rapidly growing points are situated terminally, elongation must also take place along the whole duct system. This becomes strikingly evident when the less developed ten- and twelve-year-old breasts are compared with the thirteen-year-old breast (figs 4, 5, 6) In the younger breasts, stubby branches arise very close to each other, and ridges, though present, are less conspicuous With growth of the ducts the outpouchings at the mouths of the branches become elongated and the branches themselves are farther apart. The grooves so formed are separated by ridges Beyond the opening of each branch, the particular ridges forming the boundary of the groove unite and disappear

A point that emerges very clearly when serial sections of adolescent breasts are examined is the irregularity of development in different parts of the same breast (fig 6A) In some places there will be much greater subdivisions of the ducts, and such areas persist through a number of serial sections Development is more advanced toward the muscle than near the nipple. This may be

connected with the very rich blood supply from twigs reaching the breast via the pectoral muscle.

The connective tissue of young breasts is always well developed. This is very obviously of two kinds: the intraductal, belonging to the duct itself; and the interductal, or perilobular. Interductal tissue is a supporting structure, intraductal connective tissue is an intergral part of the mammary gland.

When the breasts of a number of adolescents between the ages of twelve and seventeen are examined it is likely that nodular structures will be felt in some of them. This need not cause alarm if the normal cystlike structure of the adolescent breast is remembered together with the tendency to irregular maturation. Ducts may dilate beyond what is usual, or a cluster of lobules which has

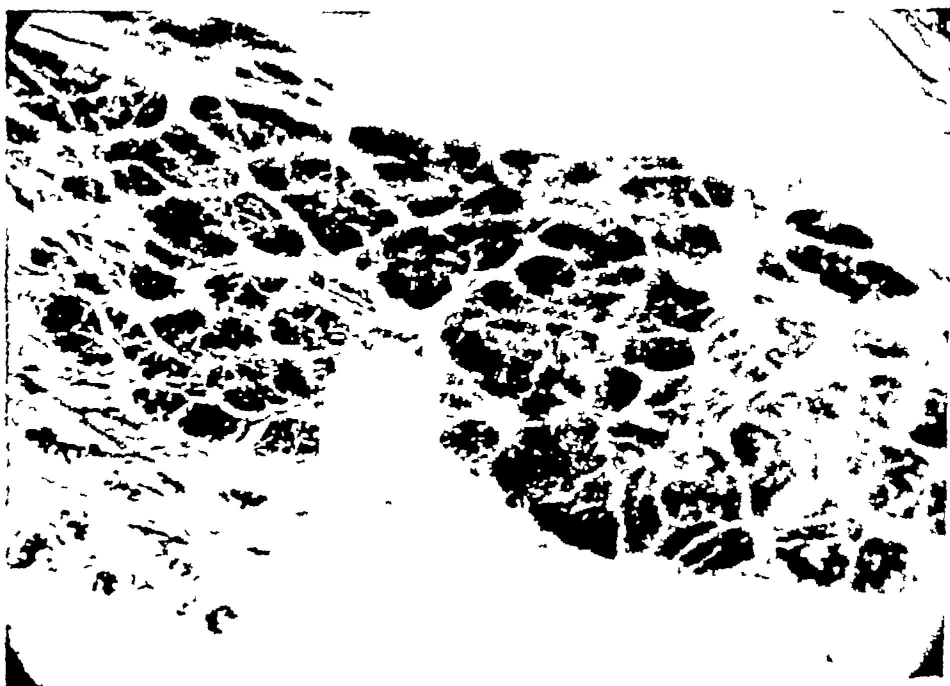


FIG. 7. Normal adolescent breast, age thirteen years Onset of menstruation ten months before death from fulminating septicemia In some parts of the breast lobules were fully developed. Other areas showed only ducts of the adolescent type Slicer section

outstripped the rest in development may feel nodular to palpation (fig 8) The possibility of fibroadenoma has to be considered, but it is usually wise to wait and see whether with further development the nodule will disappear

THE ADULT BREAST

Before embarking on a description of the normal breast certain terms in general use require clarification. Such words as trabecula, stroma, parenchyma and lobule are defined in books, but when applied to the breast there is considerable difficulty knowing just what is meant, a difficulty that most authors do not face squarely As in other organs, the breast consists of mammary tissue proper (parenchyma) and stroma. But unlike other organs, breast parenchyma is fibrous as well as epithelial Grossly, the fibrous parenchyma is impossible to distinguish from the equally fibrous stroma. Microscopically, the difference is obvious, but when a lobule undergoes involution it is replaced by fibrous tissue. It merges with the stroma and is indistinguishable from it. It is probable that much of the adult stroma is formed in this way Theoretically, this 'scar tissue" might be thought of as parenchyma, but it is nonfunctional. It does not alter with the cycle and is only a supporting structure Trabeculae are usually defined as forming an essential part of the stroma. In the breast, they run from the base of the organ to the nipple, and are conspicuous on x-ray films They consist of fibrous strands containing ducts and lobules and are therefore a mixture of all of the components of the gland. For lack of a better term, 'trabecula" is used to include both stroma and parenchyma. "Lobule ' is defined as the collection of terminal ductules arising from a duct. Lobules attain their full development during lactation At other times, especially during the menstrual cycle, they undergo changes due to hormone influence. Such changes are not necessarily regular Imperfect differentiation of ductules is common and it is often difficult to decide at what stage of development a lobule may be properly so called.



A

FIG. 8. Focal hyperplasia in a developing breast Aged 16 years. Two months ago a small red patch was noted centrally above the left nipple.

A X-ray film shows a small opacity resembling an area of adenosis There is marked vascularity of the superficial fat Marker placed at this site.

A′. Drawing from film. Arrow points to the lesion

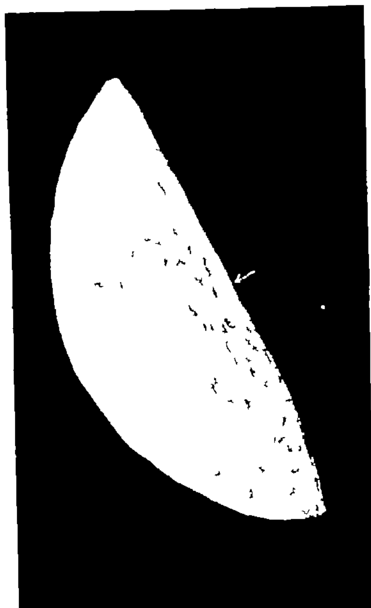


FIG 8 A

The terminological pitfalls outlined above are a reflection of the difficulties encountered in any attempt to describe the anatomy of a typical breast. The mammary gland is a variable organ even in animals In women, variability is much greater The breasts of



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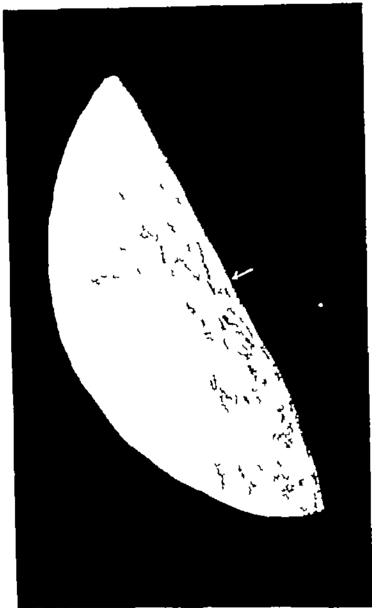


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FIG 8 B

B Slicer section shows hyperplastic area with dilated ducts. The ducts are characteristic of adolescence, but are closer together than is normal.

different women differ widely in development and structure and according to age. Individual breasts exhibit marked alterations of pattern from one part to another and continual changes are taking place in one and the same organ. The gland is never at rest. Emotional stress, allergy, or any reaction which affects the ductless glands has its repercussion in the breast Minor alterations are not detectable except in the excised specimen and, when found, it is questionable whether they should be considered physiologic or pathologic. Actually, no hard and fast line can be drawn and there is no ready-made answer to the question: What is a normal breast?

THE NONPREGNANT BREAST

In an average breast the lobules are situated chiefly at the periphery (figs 9, 24). Generally they are most numerous at the base near the pectoral fascia, probably because of the rich blood

supply to that part. In the early twenties the lobules are apt to be rather scanty and the breast is often partly of the adolescent type, especially in virgins (figs 10, 13A) The resemblance of the virgin breast to the adolescent is in great measure due to the fact that there has been no large-scale proliferation and involution of lobules with fibrous replacement as happens after pregnancy In the late twenties and early thirties there are more lobules and the difference between the parous and nonparous breast is not as obvious (figs 9, 11, 12, 13B) The lobules are irregular in contour in the parous breast and, in multiparae, there is a tendency to dilatation of prelobular ducts The lactiferous ducts may also be dilated. In the late thirties and in the forties many more irregularities are apparent in all women (figs 14, 24A) The hangovers from an earlier age are joined by the distortions due to premenopausal imbalance. Anovulatory cycles are more frequent. A breast examined in the



FIG 9 Normal breast. Age thirty two years Death from cerebral aneurism. Slicer section to show peripheral distribution of lobules No marital or menstrual history available.

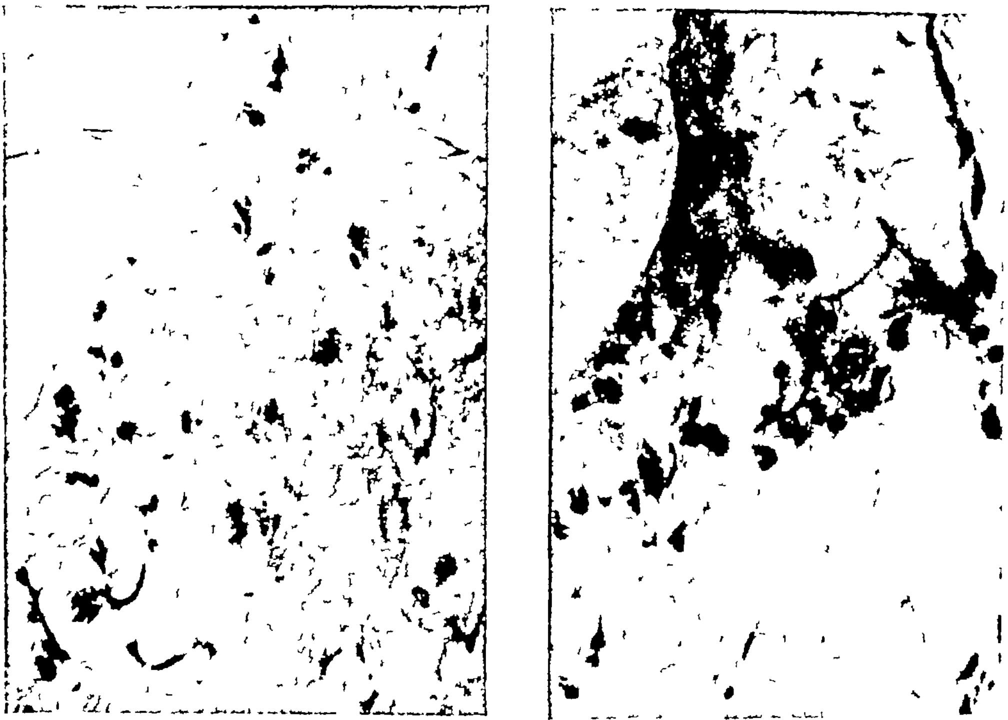


FIG 10 Postmenstrual breast Slicer sections from two separate fields. Age twenty-three years, single, death from septicemia Eighth day of cycle The breast was immature and contained very few lobules They did not show normal postmenstrual proliferation, possibly on account of severe illness
A Characteristic of greater part of breast
B Area showing the greatest lobular development.

premenstrual phase of such a cycle would show only estrin changes and might be deemed pathologic. At the time of the menopause and sometimes for a year or two after, irregular growth and regression may reach considerable proportions. The changes would in most cases be considered pathologic, but a line is not always easy to draw. Involution in these florid breasts may be expected about two years after the menopause

In view of the foregoing, the difficulty of classifying breast patterns into distinctive types is immediately apparent. The work entails cutting more or less serial sections of many normal

breasts Such material is difficult to obtain and, by most methods in vogue, making serial sections of whole breasts is extremely arduous Dabelow (1933) cut whole sections and was able to divide his material into fibrous breasts and fatty breasts, but he only covered part of the ground. Objections to his classification are twofold. In the first place, fat is not a part of the mammary parenchyma It is practically absent in the adolescent, scanty in young adults, and only begins to be an important component of the breast at the age of thirty Its presence depends largely on the state of nutrition of the subject and therefore cannot be used to identify a specific type of mammary gland. Secondly, preponderance of fibrous tissue may be normal as in the adolescent breast, but it may also be a consequence of dysplasia



FIG 11 Breast in late proliferative phase Age twenty nine years single Death from pulmonary embolism following appendectomy Although she was obese, the breast was compact. Lobules are numerous, but in about half the breast they were not well developed. Genitalia corresponded to second week of cycle.

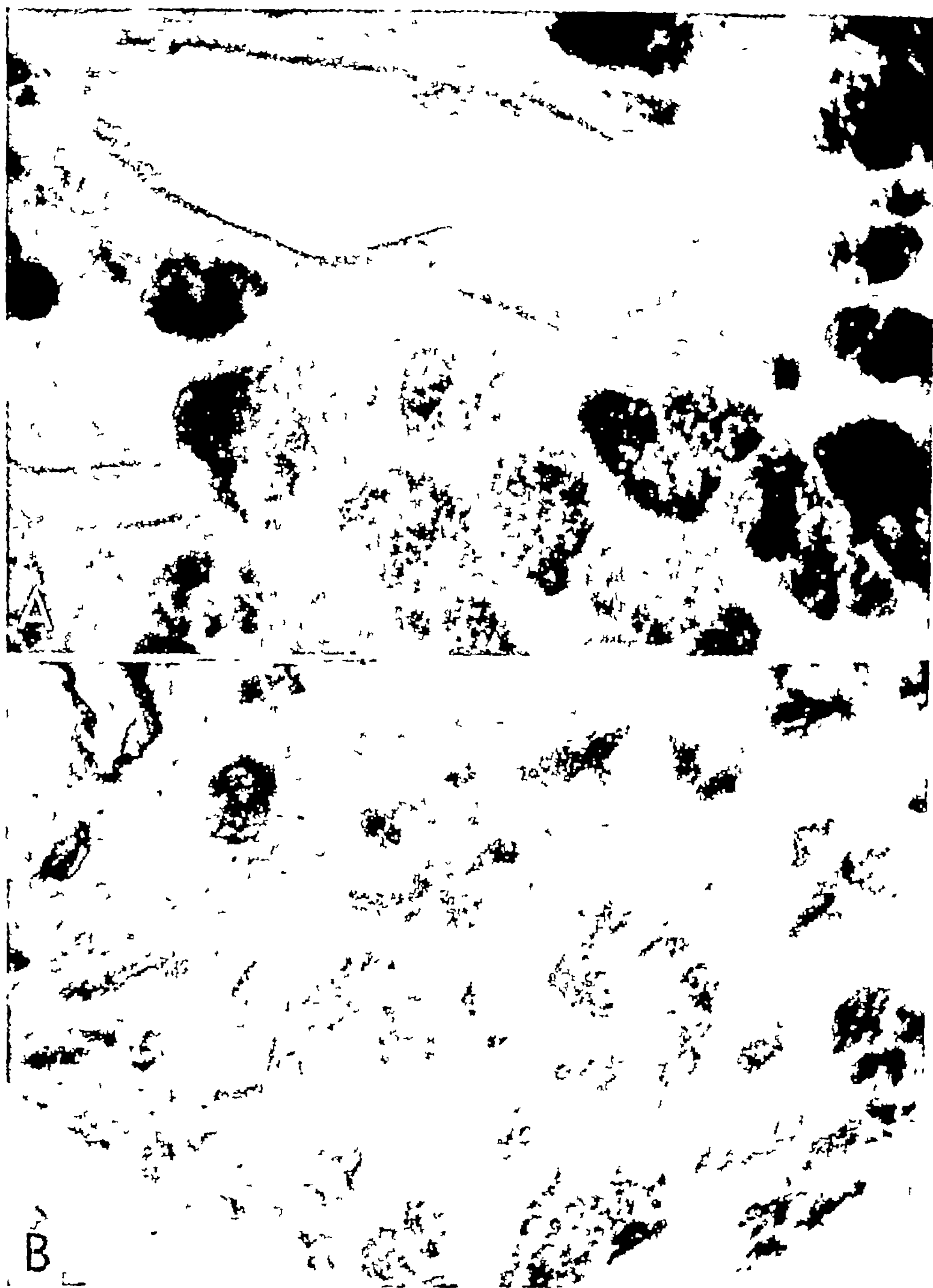


FIG 12 Variability in development of lobules Slicer sections from different areas in the breast of a married woman aged twenty-eight years She died of bronchopneumonia after two weeks illness, probably about the end of the estrogen phase of the cycle The ovaries were cystic



A

FIG 13 Comparison of immature and adult breast.
A. Immature breast ten days postmenstrual. Age twenty years There is little or no lobular development and no sign of the proliferative phase, possibly on account of illness

To facilitate examination of the entire gland we developed the slicer method and studied serial sections of twenty-seven normal autopsy breasts Seven were adolescents, twenty belonged to women aged nineteen to forty-seven years Valuable experience was gained, but the material was not enough for satisfactory analysis of breast types The pitfall in all generalizations drawn from anatomy is that there is no opportunity to study the same breast at intervals over a period of years It was only when a good technic

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FIG 12. A. Base of breast shows numerous lobules, somewhat overdeveloped for the menstrual date, and a dilated duct.
B Central area presents clusters of ducts with no acinar development. They are probably the equivalent of the Middendorp-Koenecke bodies seen in lactation. Peripherally the lobules are poorly developed compared to those at the base of the breast.

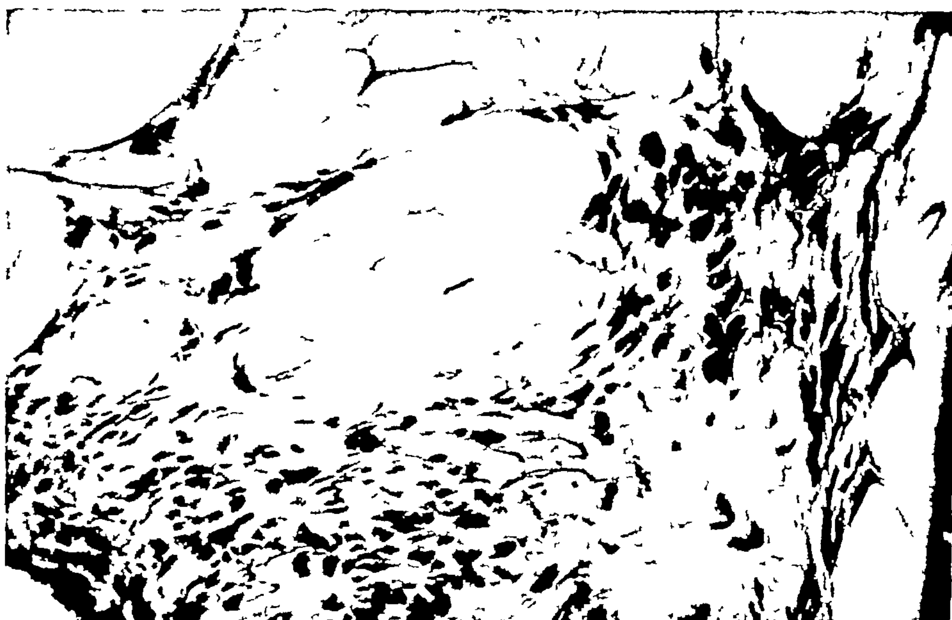


FIG 13. B

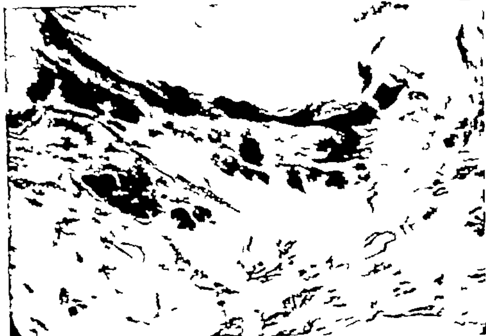
B Adult breast second day of menstrual cycle. Age thirty-nine years, married, two children

A and B are slicer sections taken at the same magnification Compare also with fig 10. The difference in the number of lobules between married and single women is striking In this breast there is slight irregularity of lobules as would be expected, but it is remarkably normal for the age

for roentgenographic visualization of the breast was developed that enough cases could be examined for a real advance to be made. Moreover, reexamination of the same subject could provide a record of individual changes A review of the roentgenograms from some 3,000 breast cases in our series showed that certain breast patterns were recognizable on the film About 2,000 cases came to operation and the specimens were available for study. Comparison of films and specimens enabled the recognition of certain breast types

Four normal types were as follows · (1) Immature (2) Glandular. (3) Involutional (4) Atrophic.

1. On the x-ray film, in girls before the menarche the gland



A



B

FIG 14. Variability in development of lobules Age forty-one years Death from intracerebral hemorrhage Fatty breast. Slicer sections, A and B two areas from the same breast to show variability in development of lobules Uterine myomas were present indicating some degree of hormone imbalance.

shows an almost homogeneous opacity. The surface beneath the subcutaneous fat is smooth. In older girls trabeculae are made out but they are thick and closely apposed (fig. 15) In the few cases where fat is present trabeculae are more easily distinguished (fig. 16), otherwise they are apt to merge and their outlines cannot be seen. The immature breast, normal in adolescence, often persists into the early twenties (fig. 17).

2. The glandular breast is that normally seen during the reproductive period (figs. 18, 19). The lobules occupy the base and peri-



FIG 15 X-ray film of normal adolescent breasts Age fifteen years The mammary tissue is dense but trabeculae are beginning to be visible.

phery of the breast, some are found in the trabeculae. The subareolar area contains only lactiferous ducts and clusters of fingerlike offshoots These are rudiments of Middendorp-Koenecke bodies which develop during lactation and will be described later On the x-ray film the principal density is at the base. In well-developed breasts it is broad and rather fluffy Similar but less dense opacities are seen at the periphery The trabeculae, which are broad with ill-defined outlines, emerge from



FIG 16 C 984. X ray film of normal breast—age eighteen years, single.



FIG 17 Immature breast. C 848, age twenty three years, single. The breast is small. It contains very little fat. The trabeculae lie close together (cf. fig. 57 illustrating a similar type of breast two days after parturition)

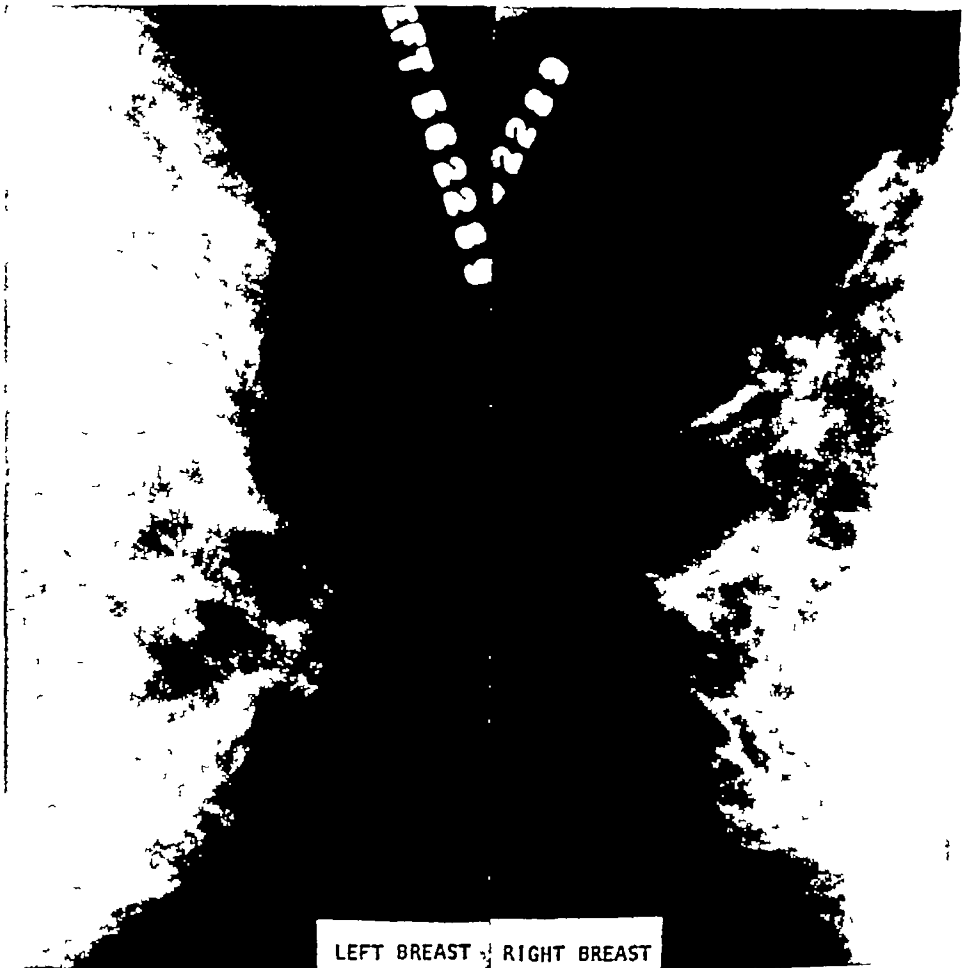


FIG 18 Normal glandular breasts Multipara, age thirty years X-ray films—left and right breasts: Glandular tissue is a little irregular and the lactiferous ducts are slightly dilated as is often seen in multiparae

the base and course towards the nipple. In the subareolar area the lactiferous ducts stand out as relatively narrow cords.

3 The involutional fibrous breast is seen following the menopause whether natural or artificial Owing to shrinkage of ducts and involution of lobules the fibrous trabeculae are sharply outlined against the interstitial fat and appear on the film as a complicated meshwork (fig. 58) If fat is not present the mammary tissue appears as a dense mass.



Fig 18. A Drawing of lactiferous ducts in left breast.

4. The atrophic breast is a sequel of Type 3 (figs 59, 60) Fat is usually deposited between the trabeculae, which become more and more attenuated. Sometimes, as in Type 3, the trabeculae are bunched together and then appear on the film as a relatively small, dense opacity surrounded by a clear zone of fat. In very emaciated old women no fat may be present.

Modifications of breast types due to dysplasia and the relationship of breast types to carcinoma will be taken up in later chapters under their respective headings

period for fifty-four days. The next cycle was twenty-six days The alterations in volume did not follow any particular rule. A case of persistent amenorrhea showed no change in breast volume except a very slight rise when she took large doses of estrogens.

Four cases of abnormal volume changes were the result of metabolic disorders. Two very obese young women had a fairly normal type of curve, but when they lost weight, one from dieting and one from illness, the breast volume dropped sharply (fig. 22). Chronic illness in two young women caused gradual

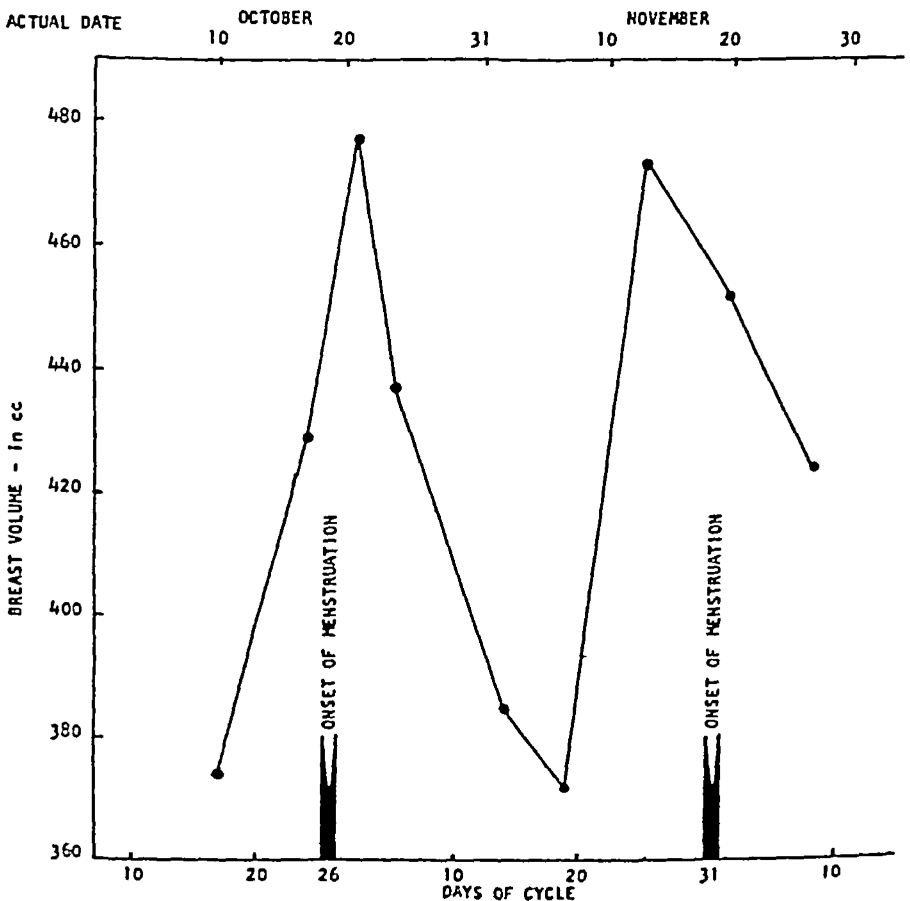


FIG 20. Volume changes during the sexual cycle.

A Age twenty-five years Volume changes during a normal cycle The lowest recorded volume is on the twenty-fourth day of a thirty-one-day cycle. However a midmenstrual rise could have been missed.

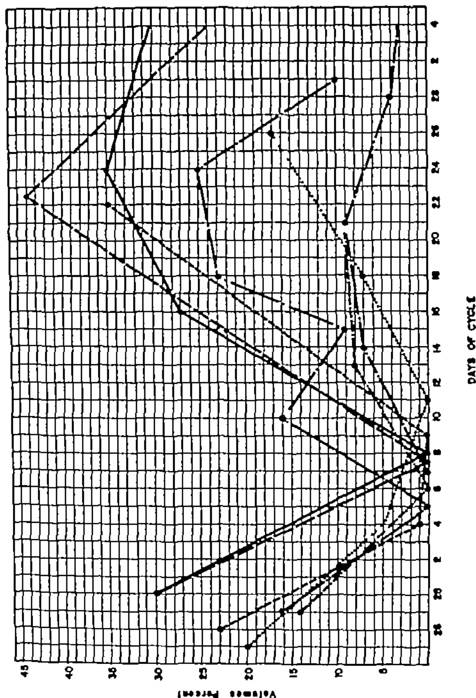


FIG 20 B Volume changes during sexual cycle in seven normal young women. For purposes of comparison the changes are calculated in volumes per cent and are plotted against a theoretical twenty-eight-day cycle.

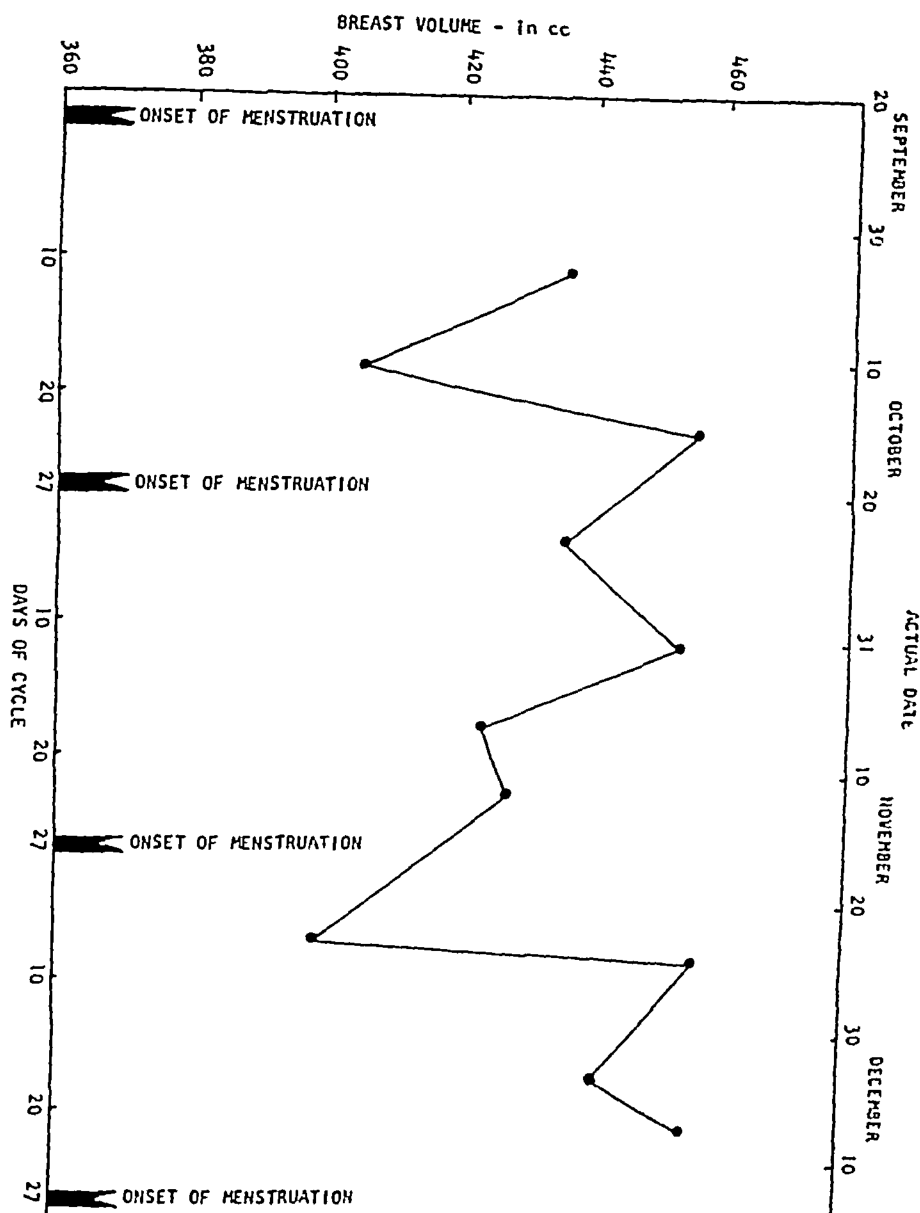


FIG 20. C Age twenty-four years Normal. Shows a rise in volume on tenth day in three successive cycles, probably preovulatory.

atrophy of the breast parenchyma. In one the curve was irregular and the glandular tissue was often difficult to feel. The other showed a steady drop in volume (fig. 23).

Measuring breast volumes is a tedious and exacting business,

partly because of the difficulty of fixing the upper boundary of the mammary gland and partly because the chest wall varies in contour from individual to individual and gives no even base for a starting point. Complete studies on patients were not possible, but while work on the normal cycle was in progress a few determinations were made on women with dysplasia. At that time, mammary roentgenography was not sufficiently advanced for accurate appraisal of the conditions encountered. Our data are often disconnected and their significance is not always clear, but they represent as far as we know the only study of its kind. We therefore append a few case histories and graphs for comparison with normal curves (Appendix I)

Lobule formation begins at the menarche (fig 7) This statement may be made categorically, assuming that the cycle is a normal one and that ovulation has taken place. We have even found a few lobules in a girl of thirteen years, who had never menstruated but

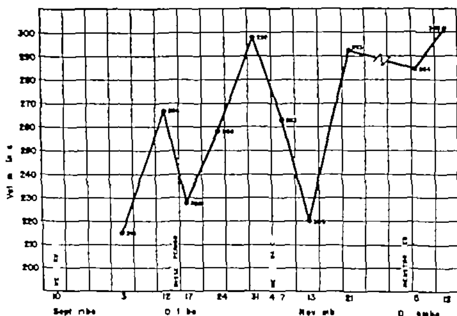


FIG 21 Volume changes during menstrual irregularity Age twenty two years Periods irregular The volume changes are erratic and do not conform to any particular pattern.

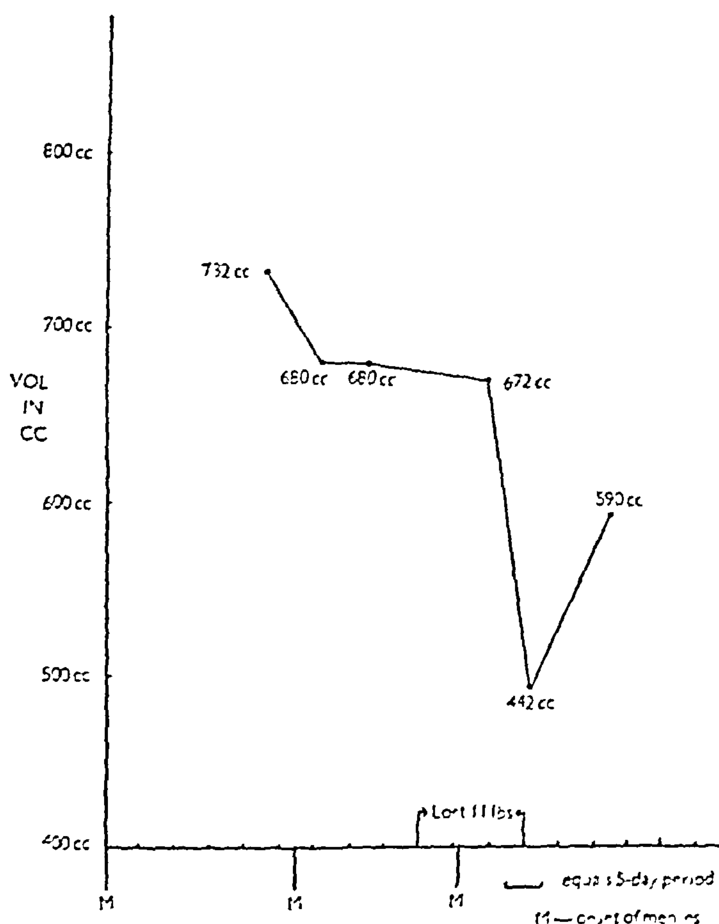


FIG. 22. Volume changes due to general metabolic disorder. Dim tion in breast volume following weight loss.

had an ovulatory scar in the ovary and a small degenerating co luteum Some authorities state that lobules develop only after first pregnancy. Failure to find lobules in the virgin breas young women could be due to a number of reasons. First, few investigators take the trouble to make and examine s sections of the entire breast. Second, it is possible that in anov tory cycles—and these may be commoner than is usually suppo —lobules do not develop. They did not do so in Speert's monk (1941) Third, in the mazoplasia of Cheatle and Cutler (mazopl fibrosa of our classification) lobules may be completely abs (figs. 95, 96).

The amount of lobular proliferation in any given breast varies enormously Because of this Speert found it was impossible to estimate cyclic changes in a series of breasts from different monkeys, but when specimens were taken at intervals from the same animal the premenstrual changes were striking and consistent. Similar experiments cannot be made in women, but with improved radiographic technic it may be possible to get an over-all idea of the alterations which take place during the cycle.

Serial whole sections of normal human breasts accompanied by a satisfactory menstrual history are few and far between So variable are they that caution must be exercised in their interpretation. Nevertheless, certain alterations do stand out. When serial sections are examined under low magnification with the dissecting microscope it is noted that the lobules are on the whole larger, denser,

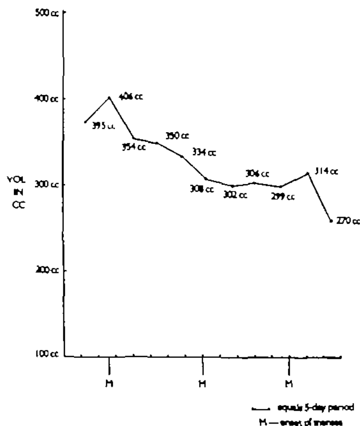
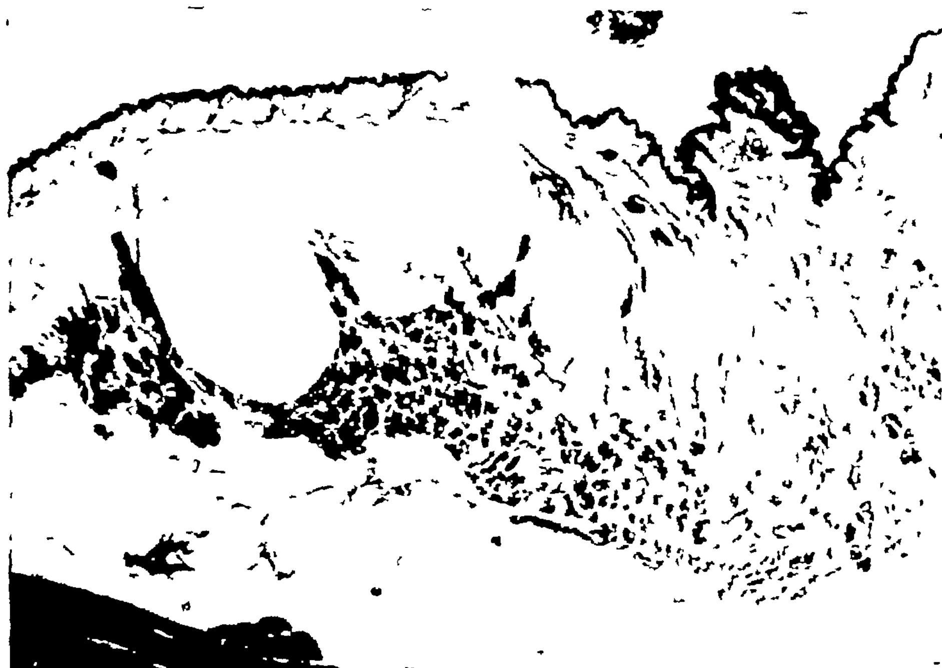


FIG 23 Drop in breast volume during chronic illness



A



FIG 24 B

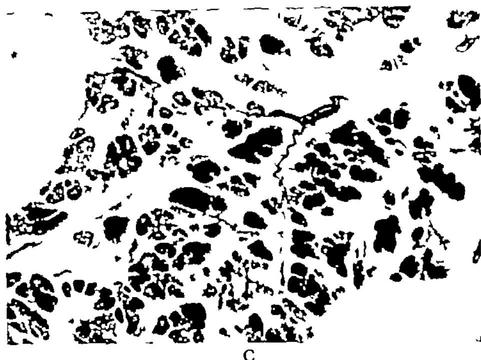


Fig 24. Normal breast. Age thirty-eight years Five days premenstrual. Single.
A. Shows distribution of lobules
B Shows nipple area. Note scarcity of lobules
C. Shows edge of breast. Most of the lobules are too dense for details of structure to be made out.

and more numerous in the premenstrual phase (fig 24) As a rule, the vascularity is increased, the prelobular ducts are slightly dilated, and the intraductal tissue is edematous

In the postmenstrual phase the lobules appear less dense because they contain fewer ductules (fig 10) Their architecture is therefore more easily discerned in thick sections It is often possible to trace the pattern of the vascular supply around them (fig 25), without special staining Judging from the specimens we have examined, the lobules are fewer in number Unfortunately, until we can find a way to examine the same breast before and after a period, full proof of this statement is lacking However, we do know that lobules undergo complete involution (fig 28) Theoretically they should be fewer in the early postmenstrual phase.



FIG 25. Vascular supply of lobule Age twenty years Ten days post-menstrual Death from T B meningitis Slicer section The breast is

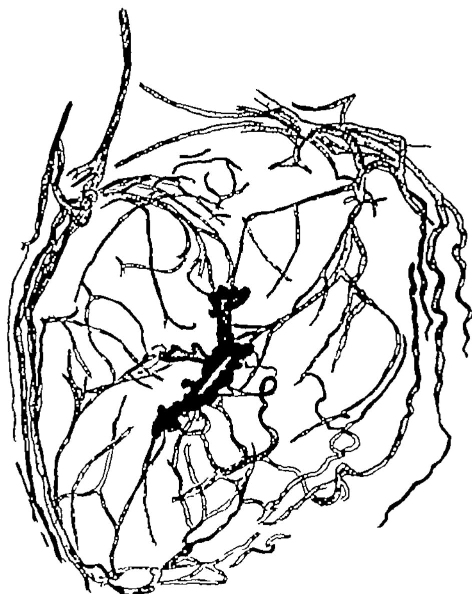


FIG 25 A

immature and probably owing to the general condition the lobules failed to proliferate postmenstrually The vessels are therefore easily seen. The arterioles form an anastomotic ring around the lobule. Abundant capillaries and precapillaries are given off to the intra lobular duct and ductules Contraction of arterioles would thus cut off the blood supply to a lobule as in the inhibitory reflex described by Cross (see under lactation).

A. Drawing from the same section to show detail of vascular supply

Minute histologic study with paraffin sections has been beset by the same confusion, due to variability in the amount of parenchyma, the number, size, and distribution of lobules, and the degree of cyclic growth and regression in different women and in different parts of the same breast. Moreover, only some lobules undergo changes during a given cycle and they may not do so simultaneously. The lobules affected by cyclic changes are generally situated at the periphery of the breast. Bearing all this in mind, we may take the following description as the physiological norm. It is based on the authors' observations from 1929 onward, supplemented by the work of Grynfeltt (1938) and Dabelow (1933).

In the postmenstrual phase there is budding out of the ductules to form new lobules The first stage is proliferation of cells at some point in the wall of a duct, probably a prelobular duct, although growth from larger ducts is also noted. Multiplication of cells takes

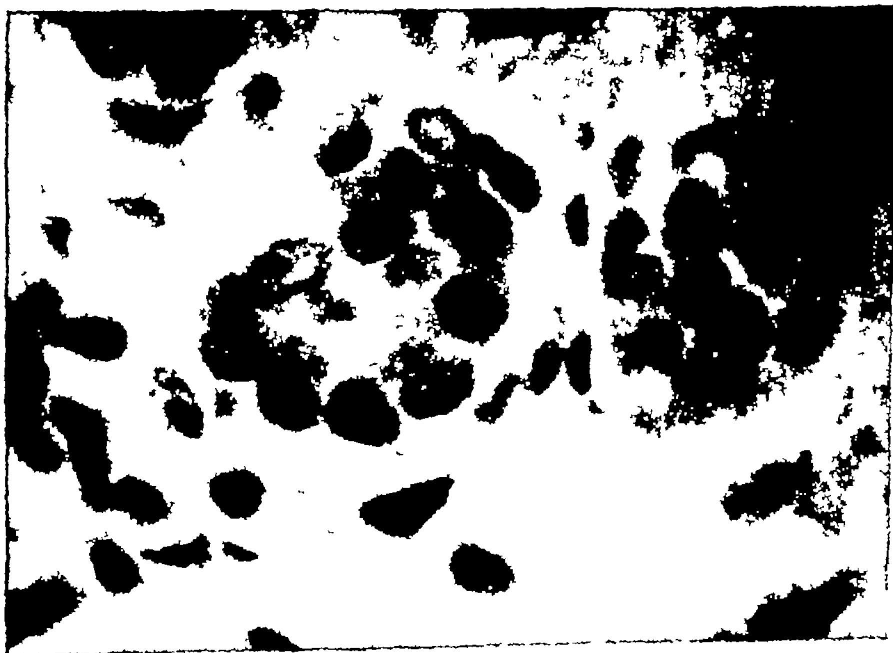


FIG. 26. Pre- and postmenstrual changes in the same breast

A. Twenty-nine days postmenstrual Epithelial nuclei are large. Owing to increase in cytoplasm they do not touch each other as in the proliferative phase

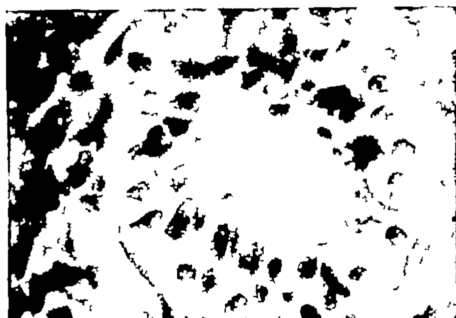


FIG 26 B Same breast three days after onset of menstruation. The basal cells are vacuolated and are about to break up Small globules of secretion are seen here and there on the surface of the epithelial cells

place by amitosis Mitosis is rare and is seen only in hyperplastic conditions Soon a lumen appears, the duct grows and ductules arise from it Growth and branching continue until a lobule is formed The epithelial cells at this stage are relatively small with deeply staining nuclei and scanty cytoplasm (fig 29) The nuclei are basal and lie close together After the proliferative phase the epithelial cells swell. The nuclei are larger and rounder and the particles of chromatin are, as it were, pushed apart by a clear substance. The cytoplasm is also increased and the nuclei are no longer in contact with each other (fig 26A) Similar changes are seen in the basal layer Granules and sometimes larger protein masses appear in the cytoplasm The protein secretion is seen first as acidophil caps on the surface of the cells Later the material forms elongated, then rounded, bodies which become detached and collect in the lumen where they fuse. Occasionally fatty secretion is also seen, but it is not to be looked for in all cases Meanwhile

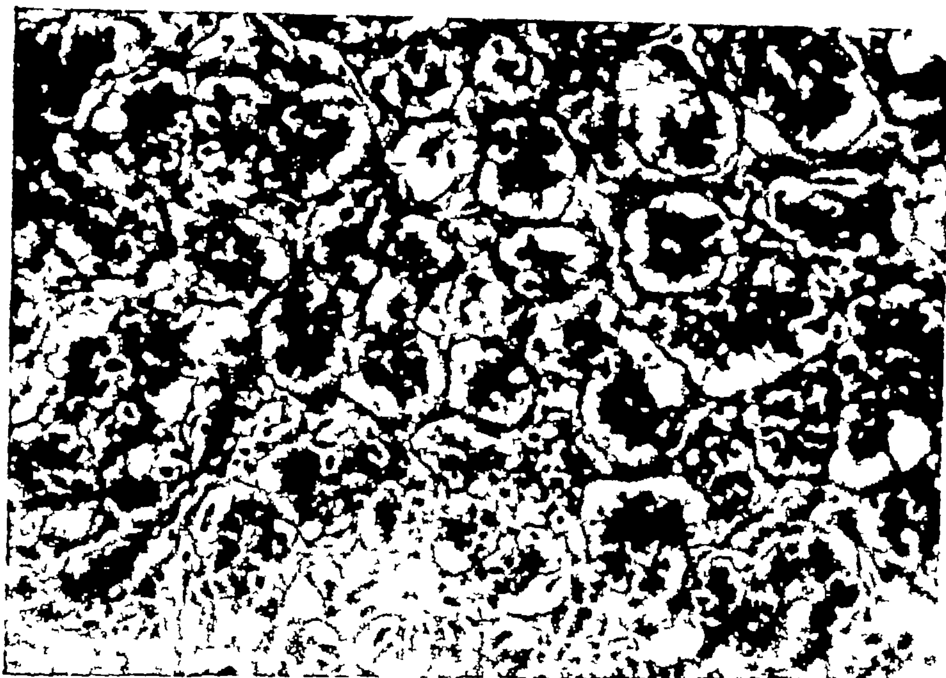


FIG 27 Breast lobule second day of a menstrual period. Age thirty-two years Sudden death from ruptured aortic aneurism The epithelial cells are shed into the lumen of the ducts Cleavage takes place along the line of the basal cells which are vacuolated and in process of disintegration

some of the basal cells show blunt processes. These elongate, become striated, and myoepithelial cells are formed (fig. 30). In the late premenstrual phase the epithelial and basal cells become vacuolated (fig 26A). During menstruation the basal cells break up and the epithelium is shed into the lumen (fig 27). In the premenstruum the pre- and intralobular ducts dilate Imbibition of fluid as well as secretion contributes to the dilatation. The intraductal tissue is loose and edematous and contains scattered mononuclear cells After menstruation it becomes dense and fibrous and fills the gaps left by the degenerated ductules

The Myoepithelium, Myothelium, or Myoid It is remarkable that in spite of an extensive literature on myoepithelial cells in German and in French dating from 1849, only three papers in English on myoepithelium in the breast had appeared up to

1950 and nothing whatever in English texts concerning its role in breast pathology Myoid cells were first mentioned by Henle (1846) and described in the sweat glands by Kölliker (1849), Langer (1871) found them in the breast. Langhans (1873) published an accurate description of the myoepithelium as it occurs normally in small ducts and discussed its origin Furthermore, he gave an account of the myoid in papilloma, cystosarcoma phyllodes, and carcinoma His observations are all the more

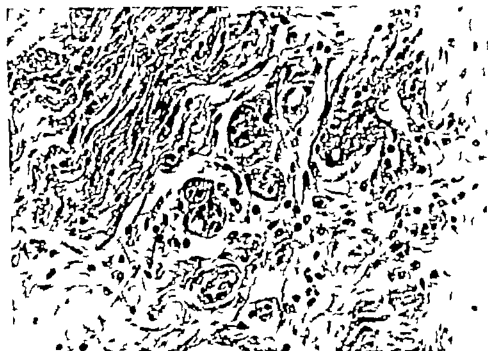


FIG 28 C 1629 Postmenstrual involution in a lobule. Age twenty-one years Operation four days after the onset of menstruation. The patient complained of a tender nodule in the right axillary tail which enlarged during her periods

Paraffin section shows a lobule undergoing involution. Epithelial cells are present in a few ducts, but are in the process of being shed. The basal cells are vacuolated. Remains of other ducts are seen in various stages of dissolution. Mononuclear phagocytic cells are present, but most of the nuclei seen belong to degenerated epithelial cells. Branching myoepithelial cells and fibrils belonging to the myothelium are visible and can be identified in several places They often overlie degenerated ducts

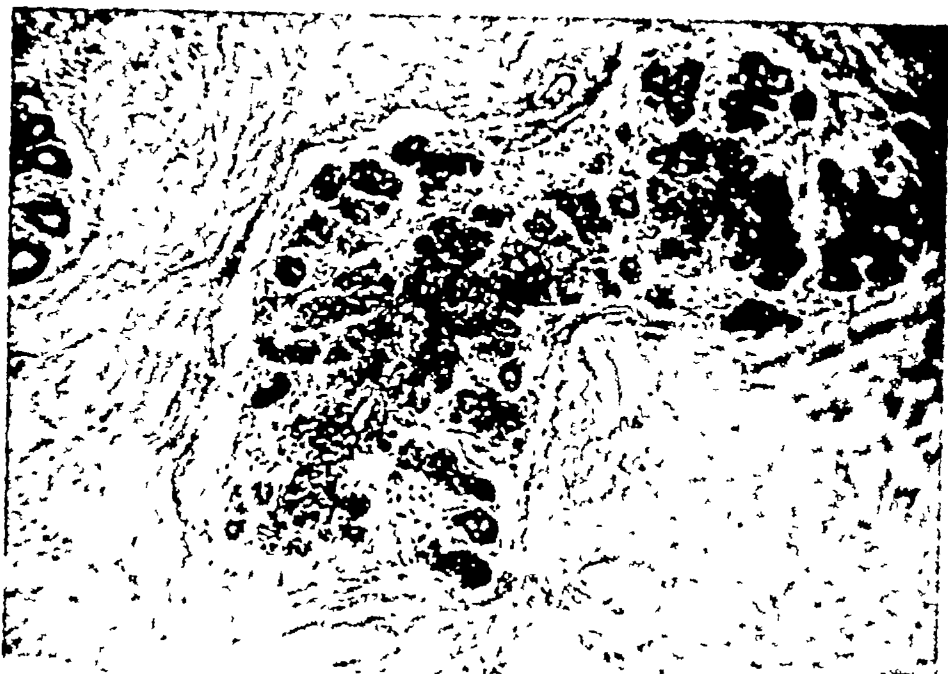


Fig. 29. Normal postmenstrual lobule. Proliferative phase, about twelve days postmenstrual. Note small deeply staining nuclei and scanty cytoplasm.

remarkable when one considers the primitive technic of that period.

The next important contribution was by Benda in 1893. He studied embryonic development of the myoepithelium and noted the occurrence of myoid cells in pregnancy and lactation. Occasional papers continued to appear on the subject, but in the 1920's there was a brilliant revival of interest due to the work of Masson (1923), Peyron (1924, 1926), and their colleagues of the French school. In 1939 a very thorough study was made by Hamperl He described the myoid in normal nonpregnant breasts, distinguishing, as the French school had done, between myoid and basal cells, and went on to a detailed examination of the myoid cells in mastopathy, papilloma, and fibroadenoma Animal tumors and malignant growths were also included Kuzma (1943) called the attention of pathologists here and in England to this very important subject.

In 1947 Rosemary Biggs drew a parallel between myoepithelial cells in the bitch and in human pathology and described their occurrence in various conditions Richardson (1949) made a study of myoepithelial cells in the lactating breasts of goats He adduced evidence of the contractile function of the myoid and in some unpublished experiments with Mavis Gunther demonstrated response of the myoid to pitocin Richardson's findings were confirmed and extended by Linzell (1954, 1955, etc.)

The normal mammary duct is lined by two layers of cells Those impinging on the lumen are cuboid to columnar and are typically epithelial. The cells of the deeper layers are more irregular in shape but are continuous A certain confusion in nomenclature has arisen concerning this layer, it is termed "basal by some, "myoid" or "myoepithelial" by others We believe that no element should be considered myoepithelial unless the cytoplasm presents one or more processes The variation in shape of the basal cell is due to its surroundings When free to expand, the cell is rounded or ovoid. Myoid cells are sparse in the larger ducts when no cause for hyperplasia is present. They lie along the basement membrane and are often found between the epithelial cells The nuclei are elongated or ovoid, sometimes triangular in cross section, and in the fully developed cell, stain relatively deeply Long fibrils are present in the cytoplasm and these course lengthwise along the duct. However, in the smaller ducts especially, myoepithelial fibrils often emerge at right angles to the lumen. In the lobules they form a network around the ductules Good preparations show occasional fibrils merging with the basement membrane. In hyperplastic conditions the basement membrane may not be visible. Instead, sheaves of fibrils emerge at right angles to the duct.

The myoepithelium is most easily observed in the lobules and more especially in the prelobular ducts (fig 30) Here the number and regularity of the basal cells depend on the stage of the cycle and on whether hyperplasia is present. A regular layer may not be visible or the cells may be multiplied and at times may even fill the lumen of the duct. In hyperplastic conditions mitoses may be seen



A

FIG. 30 C 138. Proliferation of myoepithelial cells around a prelobular duct Age twenty-eight years. A case of adenosis. Last menstrual period six days before.
A. Note fibrils in cytoplasm of proliferating myoid cells

among them. The evolution of myothelial cells in the prelobular and smaller ducts is as follows: At first these cells are plump with pale vesicular nuclei. They resemble basal cells except that, in good preparations, one or more cytoplasmic processes may be discerned The processes are blunt and irregular at first; then striae appear in them Soon the cell resembles a smooth muscle fiber, which functionally it is, its epithelial origin notwithstanding The bright red cytoplasm is easily picked out with the Goldner-Masson stain. In the smaller and prelobular ducts the myoid forms a definite layer and at times the pointed cytoplasmic processes may be seen streaming into the surrounding fibrillary tissue In lobules when postmenstrual degeneration is complete, the myoid cells are the last to disappear. Swollen degenerated elements cluster around the disappearing ductules. Their appearance suggests

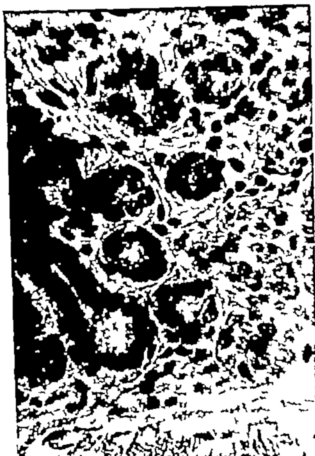


Fig 30 B Part of a hyperplastic lobule. Myoepithelial nuclei and fibrils are clearly seen between the ducts Some are emerging from the basal layer

the possibility of a phagocytic function (figs 28, 84) In ducts which do not undergo postmenstrual degeneration the next stage, although obvious in hyperplastic conditions, is hard to follow in the normal breast. However, patient search is usually rewarded by finding one or two cells emerging from the myoid into the intraductal connective tissue. Figure 30 shows a number of these cells They are elongated, with pointed nuclei resembling those of fibrocytes The cytoplasm is likewise elongated and is fibrillary Finally, there is a splitting up of the processes into fibrils which now take collagen and not muscle stains (fig 31) The nucleus becomes more attenuated and gradually disappears These observations, reinforced by studies of myoid hyperplasia by ourselves and others

We may add that we are in complete agreement with other authors when they state that there are no capillaries in the myoepithelium proper. However, with the transition to fibrous tissue, capillaries appear and are, of course, abundant.

Mammary Vessels. The main arteries supplying the breast arise from the internal and external mammary and from the intercostals. Their number and distribution is very variable. The same is true of veins (Massopust, 1950). There is no convenient milk vein as is found in dairy animals. The most constant vessel seen on our films is a vein which crosses the subareolar region at right angles to the lactiferous ducts and enlarges considerably during pregnancy. In the breasts of older women calcification of arteries is frequently observed on x-ray films just as it is in arteries elsewhere in the body.

The vascular supply to lobules and smaller ducts is an example of the correlation between structure and function which prevails in the body generally (fig. 25). Precapillary arterioles anastomose to form a circular mesh at the outer edge of the lobule or duct. They give off enormous numbers of capillaries which traverse the parenchyma as far as the basement membrane. The amount of blood reaching the duct or ductules is controlled by sympathetic fibers to the arterioles as is clearly shown by the experiments of Cross (1948) and of Linzell (1954) referred to later. The removal of epithelial debris after menstrual shedding, the presence of congestion and edema in the intraductal connective tissue, the accessibility or nonaccessibility of hormones to the mammary parenchyma may be accounted for by the state of relaxation or contraction of these arterioles. Furthermore, consideration of this factor may explain the variability of hormone response encountered in one and the same breast.

PREGNANCY AND LACTATION

The mammary gland of pregnancy shows variability comparable to the nonpregnant organ, but on a larger scale The degree of development of the gland is probably the most important factor

in determining the amount of secretion of which it is capable, and it would seem that good lobular development in the nonpregnant state would predispose to satisfactory growth in pregnancy Richardson (1949), working with goats, found a high degree of correlation between the amount of glandular tissue and the total yield of milk. Engel (1941), in a study of twenty-six women who had died intrapartum or in the first few days after delivery, classified the breasts in four groups according to the amount of parenchyma they contained (fig 32)

A. Breasts consisting predominantly of parenchyma, eight cases
B Breasts containing a fair amount of parenchyma, eight cases
C. Breasts containing an obvious amount of fibrous tissue, seven cases
D Breasts containing chiefly fibrous tissue, three cases

Our x-ray studies confirm Engel's conclusions that the yield of milk depends on the amount of parenchyma.

Palpation of the breast in early pregnancy, i e., under two months, reveals slight increased nodularity, but this cannot be considered diagnostic. At most it tends to confirm an impression gained on other grounds Halberstaedter (1948) noted uniformly diminished translucency, observed about the seventh week in patients who had been examined previous to pregnancy

Histologic examination reveals that the mammary gland undergoes changes very soon after conception The earliest specimens of pregnant breasts in the authors collection were of less than twenty days gestation. One was from a woman who died of a ruptured tubal pregnancy twenty four days after the onset of the last menstrual period. Another had an operation for multiple fibroadenomas twenty five days after her marriage. Her last period was twenty-seven days before. A third woman was operated on twenty days after the onset of the last period for a small mass in which a few dilated ducts were found. The last two patients were both nineteen years old and both showed the immature type of

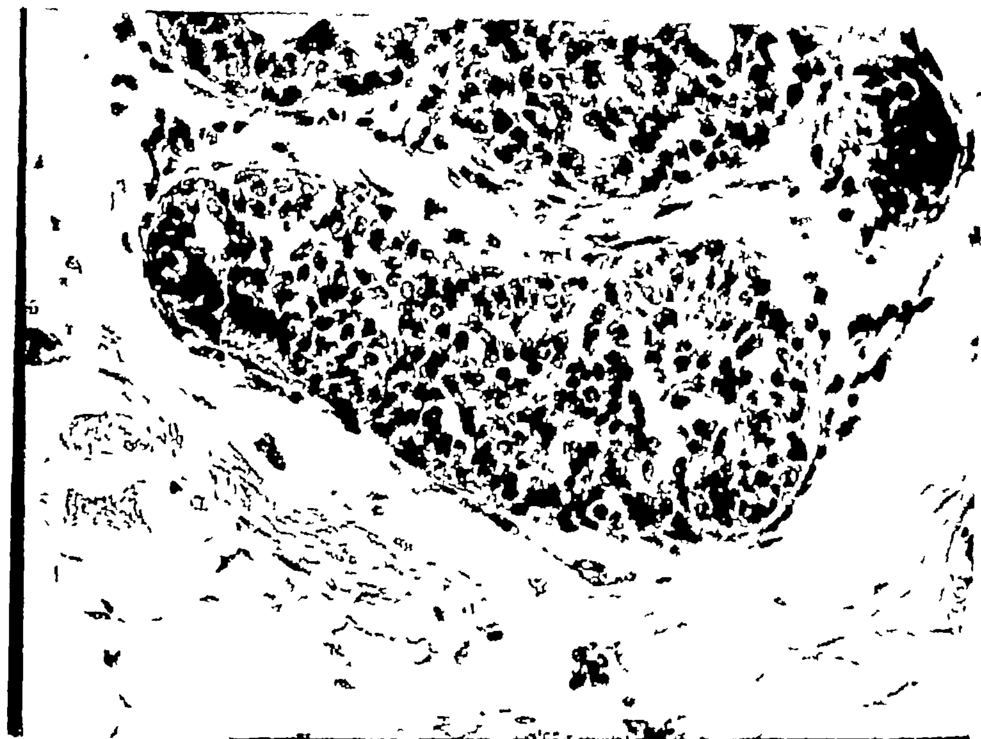


FIG 33 Breast, seven to ten days gestation.

A Age nineteen years Twenty-five to twenty-eight-day cycle. L.M.P. twenty days previous Small duct filled with proliferating basal cells The cells are still undifferentiated, but small ducts are beginning to form

earliest cases showed it in only a few places. This is in accordance with functional needs The general growth of mammary parenchyma is taken care of by less conspicuous general hyperplasia; formation of lobules is the function of circumscribed hyperplastic foci. Cell division is chiefly by amitosis, but occasional mitotic figures are seen. The primitive basal cells in these foci are large, with large clear nuclei and prominent nucleoli. The cytoplasm is abundant. A little later differentiation into epithelial and myoepithelial cells can be made out Striations appear in the cytoplasm of the myoepithelial cells and the future secretory cells begin to be arranged in rows with suggestion of duct formation (fig. 34).

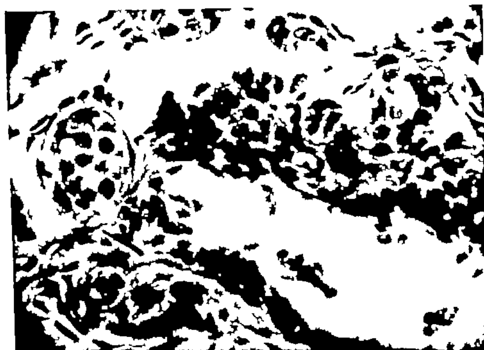


FIG 33 B Paraffin section. Foci of proliferation in a duct. Newly formed ductules are seen nearby

Edema of the intraductal connective tissue, which is probably connected with growth of the corpus luteum, is not much in evidence in the first few days of pregnancy, but soon becomes a prominent feature. A rather heavy infiltration by mononuclear cells in lobules and around the ducts is prominent in early pregnancy These cells are normally found in the late premenstrual and menstrual phases, but not to the same extent. As with other features, the infiltration occurs sporadically, but the fact that it is present without obvious cause should arouse suspicion. Careful search will also reveal branching cells with vacuolated nuclei and cytoplasm in the intraductal tissue. These cells have been described by Peyron (1932) in early pregnancy in animals, and by Brugnatelli (1914) in women. These authors called them histiocytes, but their appearance is indistinguishable from degenerating myoepithelial cells seen in the same situation in pathological conditions



FIG 34 Breast, ten to fourteen days gestation Age nineteen years. Multiple fibroadenomas. Immature breast showing very recent proliferation

A Slicer section shows early budding of new lobules along terminal ducts. The three dark patches are older lobules of which there were very few (× 11.2)

The next phase of early pregnancy was studied in three patients who had each missed one period. The first (fig. 35), a multipara of thirty-three years, believed she was three weeks pregnant. She was operated on for a large indefinite mass situated in the central part of the breast The surgeon was suspicious of carcinoma. The tumor turned out to be a pregnancy hyperplasia, occurring centrally in an area which is usually more or less free from lobules The microscopic sections showed numbers of hyperplastic lobules lying rather close together. The majority presented well-formed dilated ductules characteristic of early pregnancy. They were lined by large, often vacuolated cells The cells did not contain fat Scanty granular amorphous secretion was present,

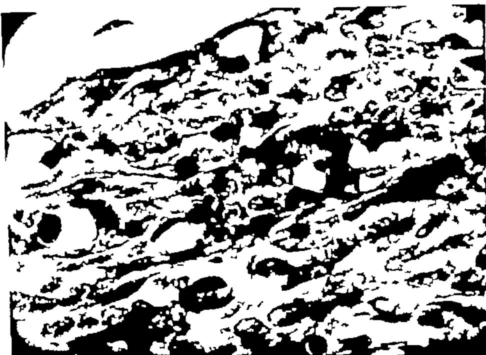


FIG 34. B Paraffin section x 400 Focus of hyperplasia with very early differentiation into epithelial and myoepithelial cells Several vacuolated cells are seen in the bottom right hand corner of the field.

containing a very occasional fat droplet. The epi- and myothelial cells were obviously active. In other lobules there was tremendous proliferation of cells intermediate between epithelial and myothelial. The nuclei were large, with prominent nucleoli, and could easily have been mistaken for those of carcinoma. But further study revealed that some cells possessed elongated cytoplasm with fibrils characteristic of myoepithelium, while others were in process of forming small ducts In some fields the developing ducts were surrounded by a dense feltwork of myoepithelial cells Every stage of the process, from the jumble of embryonic cells to orderly lobule formation, could be followed in these sections The intraductal tissue was edematous In the more differentiated areas sheaves of fibers from the myoid cells could be seen passing into it. Large and small lymphocytes were present together with a few

plasma cells, but the infiltration, although more uniform, was less dense than in the earlier cases. Vacuolated branching cells were occasionally seen.

Another woman (fig. 36), aged twenty-four years, was operated on for a small fibroadenoma. Her last period was forty-eight days before. The paraffin section presented a variety of changes similar to those seen in the previous case, but the hyperplasia was not as great.

The third case is an example of the difficulty of recognizing early pregnancy in the presence of other changes. The woman was a twenty-five-year-old multipara with five children ranging in age from seven years to fifteen months. She had been nursing up to a short time before the operation and was unfortunate enough to have her breast removed under the impression that she had a carcinoma. The other breast had been amputated at the age of nine years for childhood hypertrophy. The previous menstrual period was five weeks before. The breast showed a fibroadenoma, pregnancy hyperplasia, and lactation involution. The lobules were large. In them some ductules were degenerating and were in course of fibrous replacement. Others presented cells with the large clear nuclei characteristic of hyperplastic basal cells. There was much lymphocytic infiltration, but since this is seen in lactation involution as well as in pregnancy hyperplasia, it did not help the differential diagnosis. The over-all hyperplasia was obvious in the serial slicer sections. The paraffin sections showed numerous small isolated focal hyperplasias in the breast and in the fibroadenoma. Nevertheless, in the absence of history and without experience of

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FIG. 35. Breast, three weeks gestation. Age thirty-three years. Multipara.

A Hyperplastic lobules Note myoepithelial proliferation.

B. Early stage of myoepithelial proliferation. Note large nuclei with prominent nucleoli. Fine fibrils can be discerned in the cytoplasm of most of the cells

C Shows slightly more advanced differentiation Early acinar formation can be made out



A

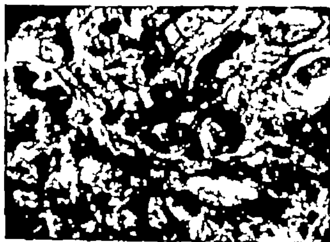
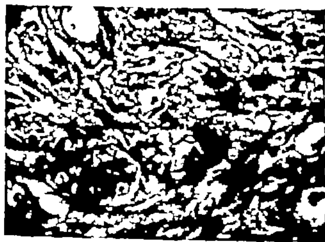


Fig 35

B



C

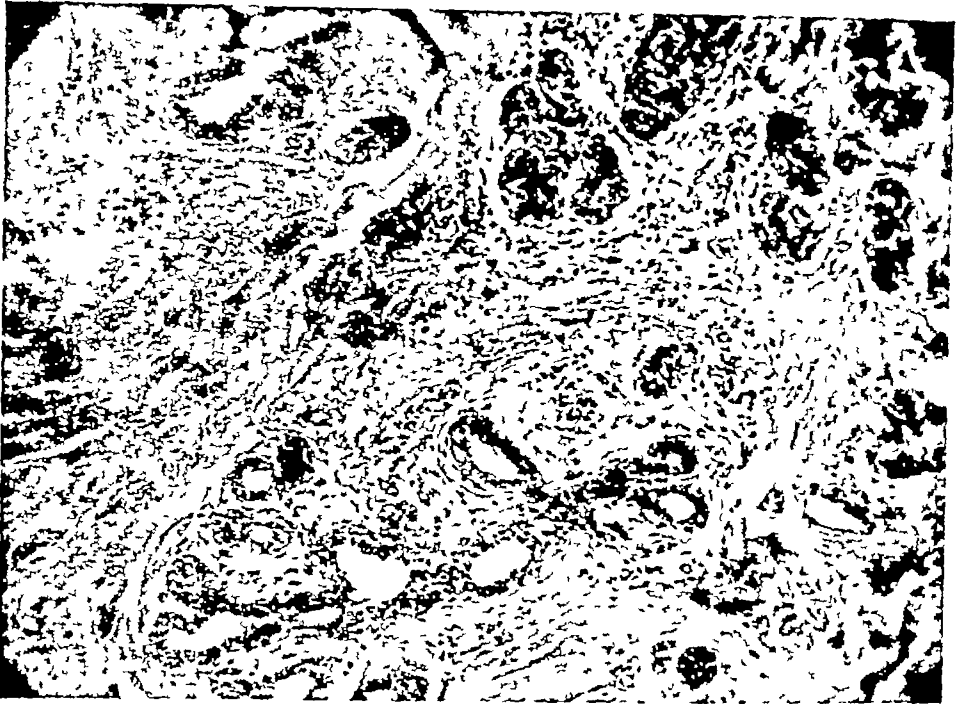


FIG 36 Breast, five weeks pregnant Age twenty-four years.

A One lobule shows dilated ducts with terminal budding In the upper part of the section there is marked cellular proliferation. Vacuoles appear in some of the cells. The lobular tissue is edematous and contains mononuclear cells Paraffin section × 100

other cases, early pregnancy would not have been recognized (fig. 37).

In the third month of pregnancy lobular development varies considerably in different parts of the same organ (fig. 38). This is true of any stage of pregnancy, but is perhaps more striking at this time In many places the duct pattern recalls that of the adolescent, but this resemblance is only in outline. When the clumps of slightly dilated, club-shaped terminal ducts are examined under high power, it is seen that the epithelial cells are large and vacuolated. The majority are loaded with fat (figs 38, 39) This is of interest because, in the later months of pregnancy, the intracellular fat is often less (fig. 40) At term, many cells show only a

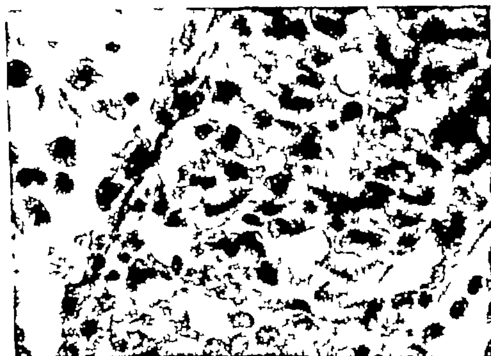


FIG 36. B Shows details of intraductal proliferation with early acinar formation. Paraffin section × 400

few fat globules (fig 41) The explanation may be that the fat is excreted into the ducts during the formation of colostrum At three to four months, myoepithelial cells are abundant. They are seen growing out in many places from the walls of the terminal ducts In many the cytoplasm is elongated and fibrillary, but others contain large globules of fat like those of the epithelial cells (fig 38D) Hamperl (1939) called attention to fatty degeneration of myoid cells in hyperplastic areas The cells degenerate and leave a round space in the tissue as seen in paraffin sections A similar process takes place here Round holes, sometimes confluent, are seen just outside and also in the epithelial layer In the loose fibrillary area surrounding the developing glandular tissue more differentiated myoid cells are seen, as well as thin-walled capillaries and scattered mononuclear cells In the more fully developed areas there are large lobules with well formed acini in which practically all the

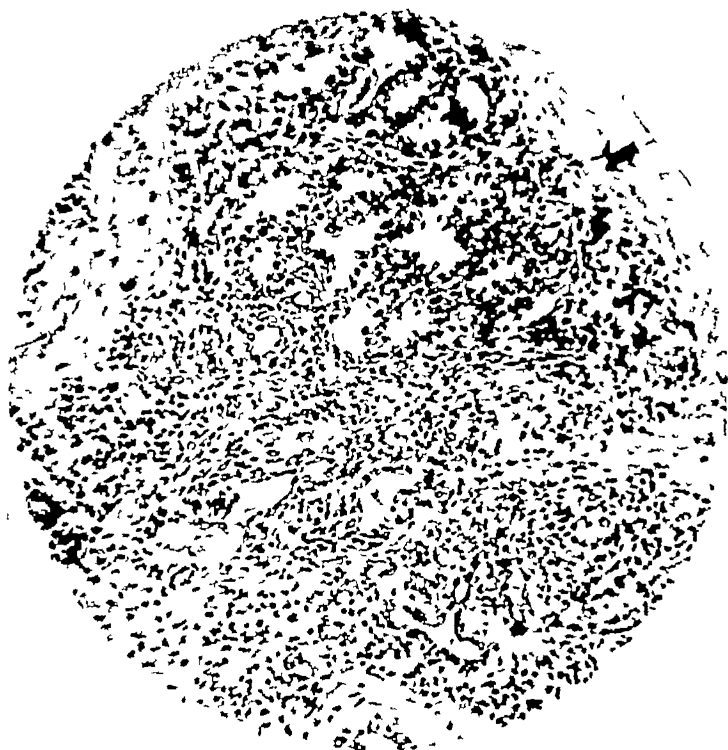


FIG. 37 Early pregnancy hyperplasia with lactation involution Age twenty-five years L.M P. five weeks before Paraffin sections.

A The upper part of the figure shows lactation acini in process of involution (arrow). Elsewhere irregular ductules are surrounded by fibrous tissue and mononuclear cells.

cells are loaded with fat In these areas and as pregnancy progresses, paraffin sections show abundant fibrils of the myoid together with one thin-walled capillary filling the narrow space between the acini. Actually, as is seen in thick preparations, the acini are surrounded by a capillary network, but only one vessel is seen between adjacent acinar walls. As Linzell (1952) has observed, the myoid nuclei often lie close to the capillary wall Even in these lobules growth is still taking place, as is shown by occasional small clumps of undifferentiated cells with primitive myoid cells among them

In the later months of pregnancy, as the lobules develop, a

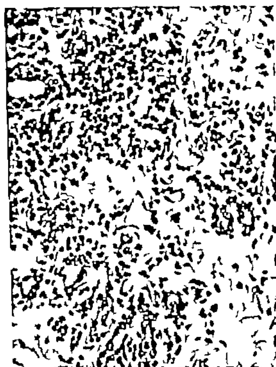


FIG 37 B Proliferating ducts, many of which are lined by epithelial larger cells than in the normal nonpregnant breast. The same confused appearance prevails as in A. The sections illustrate the difficulty of diagnosis of early pregnancy in the presence of other changes.

larger proportion of the myothelium is differentiated, but its essential characteristics are unchanged. Clusters of primitive myoid cells are still seen between the acini in many places The differentiated myoid cells are larger than in the nonpregnant breast. Their long fibrils can be traced for considerable distances They often replace the basement membrane and may lie between the epithelial cells In cross section they are seen as dark particles, not unlike very small nuclei. The impressive hypertrophy of the myoepithelial cells at this time is a preparation for their ultimate function in lactation (fig 45B)

Discharge of colostrum from the nipples during pregnancy is common. Occasionally it happens that the colostrum secretion



A



B

FIG. 38 Breast, three and a half months pregnant Age thirty years Death followed fractured skull from a fall

A. Slicer section shows unequal distribution and development of lobules.

B Paraffin section, low power The epithelium is vacuolated The intralobular duct contains secretion



C



FIG 38 D

C. Frozen section, hematoxylin and Scarlet R. The epithelial cells are loaded with lipoid.

D Paraffin section. Large vacuoles representing remains of fat-distended myoepithelial cells are seen lying on the basement membrane. Similar vacuoles are found here and there in the intralobular tissue.

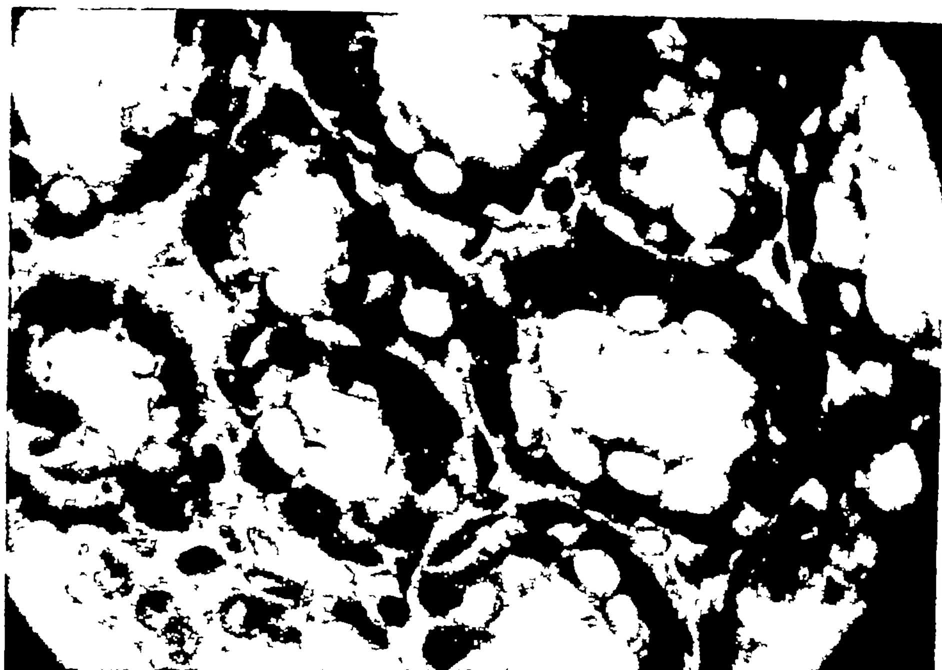


FIG. 39 Three months pregnancy. Age twenty-five years. Note vacuoles due to fatty globules in epithelial cells There is a close resemblance to the secreting breasts of infants (see fig 3). Paraffin section

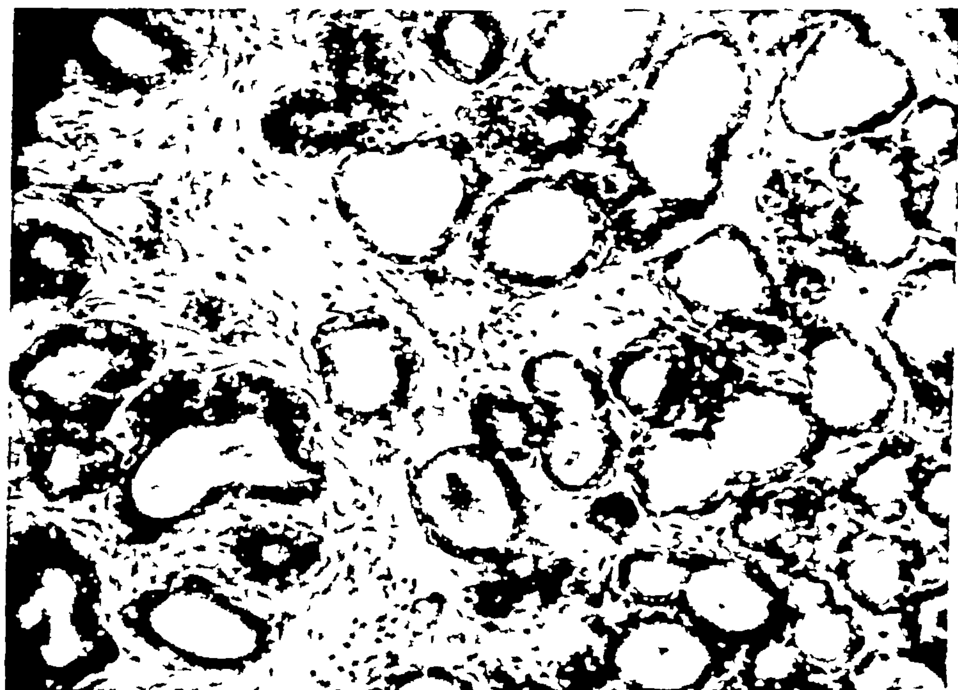


FIG 40 Seven months pregnancy. Age twenty-two years The epithelial cells contain less fat than at three months gestation (Paraffin section, low power.)

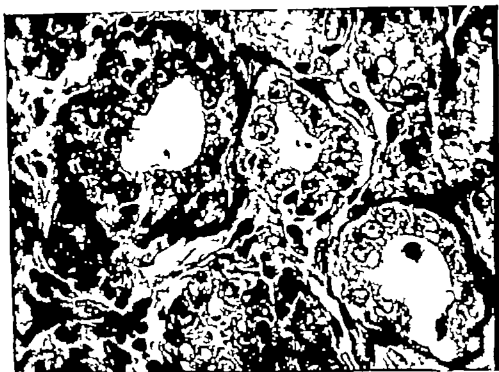


FIG 41 Breast at term. Age fifteen years Nine months pregnancy Admitted with primary eclampsia. Death thirty hours postpartum. Some of the acini contain colostrum. The lining epithelial cells contain a few fat granules, but only occasional fatty globules The myoepithelium is well developed. (Paraffin section, × 1000)

either before or after parturition contains a small amount of blood Cows, and especially heifers, often show this, and in them it is considered a sign of a good milker Two such cases came under our observation. One woman, aged twenty-eight years, was five months pregnant. She complained of bleeding from the right nipple and a yellow discharge from the left nipple. On examination the lactiferous ducts of the right breast were palpable. Pressure on one duct above the nipple produced a small drop of blood A drop of clear discharge could be expressed from below the nipple. The left nipple exuded a minute amount of milky fluid following compression of the ducts Examination of the bloody discharge showed a number of large epithelial cells characteristic of pregnancy No

fragments resembling papilloma were found. The colorless discharge contained colostrum cells, as did the discharge from the left breast. X-ray films of right and left breasts showed dilated lactiferous ducts especially on the right side (fig. 44). At operation the duct containing blood was excised Sections showed marked pregnancy hyperplasia but no papilloma (fig. 45C and D).

The second case was of a woman twenty-nine years old, who was seven months pregnant She had a colostrum discharge from both nipples for three weeks, and had noted a small drop of blood from the right nipple two weeks previously. Smears of the discharge showed large numbers of colostrum cells and, in one film, a few degenerated red cells. X-ray films were characteristic of seven months pregnancy (fig 46A) No tumor was discerned. A diagnosis of "probable erosion in a lactiferous duct, following

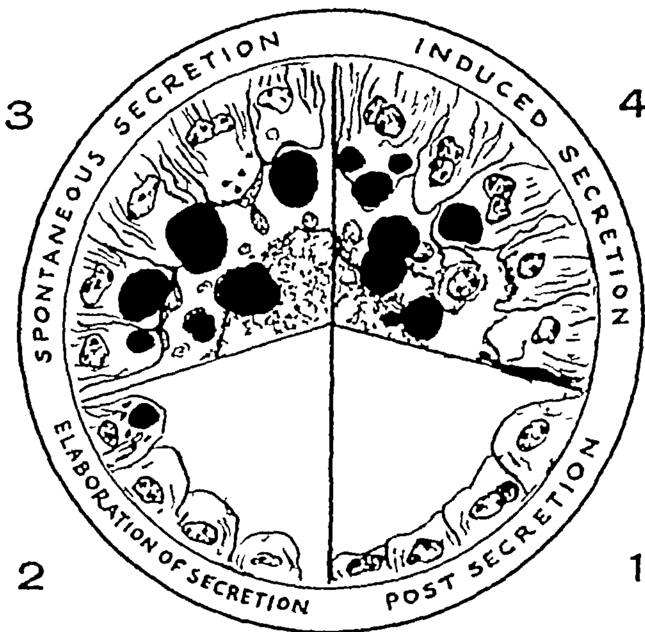


FIG 42 Diagrammatic drawing of secretory process (after Grynfeltt) (2, 3, 4) *Represent the secretory process within the cells* (1) Shows low cuboid cells immediately after secretion Grynfeltt believed that secretion was "induced" more rapidly during suckling and that the cell membrane might therefore be ruptured at this time. His explanation has been disproved by modern work

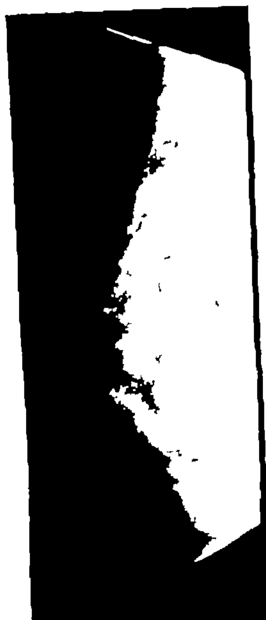


FIG 43 C 587 Early pregnancy Age thirty two years. Two and one half months pregnant. The trabeculae are uniformly thickened throughout the breast and are rather fluffy The basal opacity is increased. A somewhat similar increase in density is seen on the x ray film in cases of adenosis, but the hypertrophy is irregular

Cf figs 48 and 57 (similar types of breast two days postpartum) also figs 17 and 177



FIG. 44. Five months pregnancy. Discharge from both nipples. Age twenty-eight years. Primipara. She had bloodstained discharge from the right nipple and abundant yellow discharge from the left nipple. Dilated ducts were palpable beneath the right nipple, but none was felt in the left breast. A smear from the right nipple showed red cells and larger epithelial cells characteristic of pregnancy, but no fragments diagnostic of papilloma. Smear from the left nipple showed only colostrum

A. Left breast Lactiferous ducts are dilated. Breast trabeculae are indistinct and partly coalesced.

B. Right breast. X-ray film shows markedly dilated lactiferous ducts, marker placed over swelling



FIG 44. B

B Drawing from x ray film showing outlines of dilated ducts The smooth walled structure in the lower part of the breast is a dilated vein (arrows)

congestion incidental to pregnancy" was made Three months after parturition the patient returned for a check-up The x-ray film showed a normal breast in the late stage of lactation involution (fig. 46B)

Roentgenographic detection of pregnancy before the third month depends on comparison with a film of the same patient taken in the nonpregnant state. Of course, this is not usually



A B

FIG 46 C 948 Breast before and after parturition Age twenty-nine years.

A Seven months pregnant Colostrum discharge from both nipples for three weeks The breast had a homogeneous "ground glass" appearance. The lactiferous ducts are dilated, "d "

B. Same breast three months after parturition The patient did not nurse. Trabeculae are now clearly visible. Several fluffy patches are scattered over the breast, the remains of pregnancy hyperplasia

films the extremities of the pyramids are rounded or even flattened. In breasts with well-developed parenchyma the trabeculae are contiguous throughout and extend in one dense mass whose components are indistinguishable until they are close to the skin. Here the mass presents shallow digitations with a crenated or scalloped outline. In most films the trabeculae, whatever their type, are uniform throughout the breast. Occasionally, however,

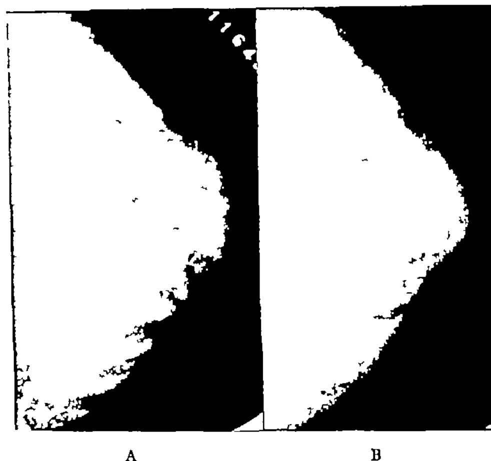


Fig 47 C 1164. Breast before and after parturition. Age seventeen years.

A. Late pregnancy Breast thirteen days before parturition. X ray film shows a dense breast, having the characteristic "ground glass appearance. The lactiferous ducts are dilated and tend to overlap Sacculi are present but not clearly defined. Beneath the subareolar region is a row of well-defined pyramidal digitations

B The same breast two days post partum. The baby had been nursed for five minutes from each breast. The breasts were turgid and milk exuded from the nipples. The x ray film shows a much larger breast. The digitations are now very broad and tend to merge. The subareolar area is distended with opacities which probably represent dilated ducts

more than one type is present. As the breast increases in size the parenchyma is pushed out toward the skin and replaces the normal fatty layer. In a turgescent breast it is possible to see ripples on the surface which correspond to underlying digitations.

Dilatation of lactiferous ducts is a constant feature in pregnancy and may be visible in primiparae as early as the second month. In multiparae, dilatation is often present in the nonpuerperal state (fig. 18), and is therefore not significant. From about the fourth month onward, rounded or irregular opacities begin to appear in the subareolar region As gestation proceeds these structures become larger and, in conjunction with dilated ducts, cause bulging of the subareolar area. They will be described more fully in connection with changes observed during lactation.

Secretion of Colostrum and Milk. Lactation involves three processes: secretion of milk by the alveolar cells, propulsion of milk from acini to ducts, and emission or ejection of milk from the breast by suckling or milking. All three have been the subject of intensive research, and although some points remain to be settled the chief features of milk production are now understood.

In early pregnancy there is secretion of protein into the ducts similar to that found in the premenstruum but more abundant. Later, at the third or fourth month, fat becomes intermingled with the protein The secretion, known as colostrum, may be discharged from the nipple during pregnancy More often it appears after parturition Colostrum differs from milk in the respective proportions of fat and proteins as well as by its high calcium content. It also contains a variety of cells, summarized as epithelial cells, wandering cells, and colostrum corpuscles. It is around these last that controversy centers Also known as granular bodies or corpuscles of Donne, they appear, when fully developed, as very large, more or less rounded cells with small nuclei The cytoplasm is stuffed with fatty granules There are also fatty vacuolated bodies without nuclei These may be degenerated cells or merely aggregations of lipoid granules The corpuscles of Nissen, which may appear similar in paraffin sections, consist of a degenerated nucleus

and abundant cytoplasm crammed with protein granules Grynfeltt maintains that colostrum corpuscles have nothing to do with shed epithelial cells—they are wandering cells (histiocytes) which have migrated into the ducts Engel, on the other hand, believes they are of epithelial origin and only a minority are "wandering cells" We agree with Engel that both origins are possible, but that the majority are derived from the epithelium At full term and just after delivery the epithelial cells may contain relatively little secretion. In one patient dying of primary eclampsia thirty hours after delivery, no lipoid could be seen in many of the cells (fig 41) In two others, dying of postpartum hemorrhage one hour and thirty-two hours after delivery, respectively, there was much less lipoid in the acinar cells than in those of two women who were eight months pregnant.

Material from normally functioning human breasts in full lactation is difficult to obtain and even more difficult to preserve without distorting the tissue. We are accustomed to thinking of secretory cells as tall and prismatic and "resting" cells as lower and more or less cuboid in shape. But if there is pressure from accumulation of milk in the alveolus, the alveolar wall will be stretched and the cells may appear broader and flattened How far can this process go without affecting secretion? When a piece is removed for histologic section the milk runs out and the pressure within the alveoli is suddenly released. This may lead to destruction of the cells and changes in their shape. Postmortem dissection is not free from objections Removal from the body entails considerable distortion in shape, and satisfactory fixation for histologic purposes is difficult. Moreover, except in sudden accidental death, a woman in extremis is unlikely to be nursing Perfusion and fixation in situ, the only satisfactory method, is not practicable in humans We are therefore compelled to use animals Much of our knowledge stems from researches made in connection with the dairy industry

Mammary secretion is of the merocrine type and resembles that of salivary or sweat glands in that, as regards the nucleus, the acinar

cells remain intact. The histology has been described in detail (fig. 42) by Grynfellt (1937), from animal and partly from human studies. An excellent account is given by Folley (1952). Important work has been done by Richardson and Linzell. As in other glands, all acini are not equally active at a given time. While one group of acini is secreting, the epithelial cells are re-forming in another area. The cells of individual acini, however, are more or less uniform as regards their secretory state. After secretion has been discharged, the alveolar cells are low cuboid. With rebuilding of secretion, striae due to currents caused by dialysis of interstitial "plasma" into the cytoplasm appear at the base of the cell. Minute particles are formed along the striae. The cell swells. The products of secretion, protein and fat, accumulate in the supranuclear zones, which now form rounded or conical projections. During the active phase the cells project into the lumen of the acinus. Their apices are domelike or hooded, due to globules of secretion pushed up beneath the cell membrane. The question of whether rupture of the cell membrane occurs during extrusion of this material is still being debated During pregnancy, fat and protein are certainly able to pass though the intact membrane, but at that stage the process is a much slower one. Grynfellt held that, between periods of milking or suckling, secretion passed through the intact cell, but that with rapid emptying of the alveoli the cell membranes were apt to be ruptured A few cells might even be shed in the process. Grynfellt believed that suckling caused increase in secretion. Modern observations with isotopes contradict this (Williams and Turner, 1954) During the intervals between suckling or milking the secretion accumulates in the ducts.

Roentgenography has been used with considerable success in studies of the anatomy and physiology of the postpartum breast. Excellent illustrations of ducts visualized by contrast mammography showing the transition from pregnancy to lactation have been published by Leborgne (1953) Mammography can be done without harm to the patient and the procedure is not painful when properly carried out. However, our objective differed from that of

Leborgne in that we set out to study physiologic changes in a very labile organ and were thus precluded from taking any measure which might interfere with normal reactions No artificial aids were used, and we relied on good technic to produce satisfactory visualization of parenchyma and ducts Our conclusions are based on study of seventy-nine sets of films from sixty-five normal women. The films were taken during pregnancy, after parturition, during suckling, and when involution had begun. Occasionally we were fortunate enough to have roentgenograms of a patient taken before she became pregnant. Figure 50 illustrates a series in which x-ray films were obtained before, during, and after the gestation cycle

Immediately following parturition the breasts are relatively flabby and appear less dense on the x-ray film. But as secretion builds up there is obvious increase in size and density (fig 47B) The distended breast encroaches on the superficial fat and may press on the overlying skin. Except in fatty breasts the posterior two-thirds of the gland appears solid, and digitations when recognizable are almost always confined to the anterior third. Their arrangement is mostly irregular, their borders are not clearly outlined, and their apices are often blunted. After suckling, their appearance changes They are often widely separated and their outlines are irregular and ragged (figs 48, 49) The areola presents a rounded surface due to dilatation of the underlying structures The most interesting changes are seen in this area.

Roentgenograms of the nonpregnant breast show the lactiferous ducts as thin cords running toward the nipple and losing themselves in the fibromuscular pad (fig 18) During pregnancy they dilate and become slightly beaded Toward the end of pregnancy other opacities, sometimes rounded, sometimes irregular in outline, appear in the subareolar region. Some of these are discerned as outpouchings from the ducts They vary considerably in size and numbers in different women and on the whole are proportionate to the degree of parenchymatous development in the breast. After parturition the breast increases in size and all the structures in the

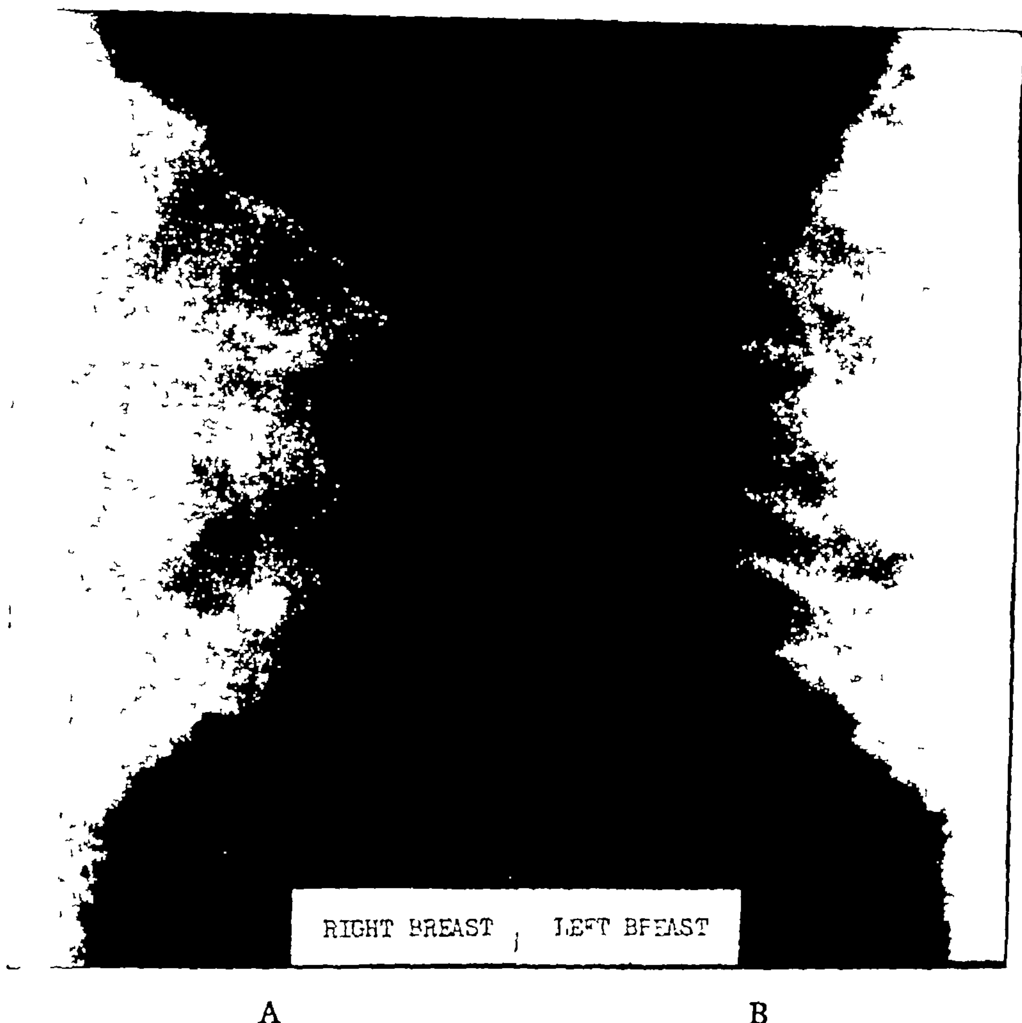


FIG 48 C 1257 Right and left breasts at the onset of lactation Multipara, age thirty-five years, two days postpartum The milk came in a few hours before the film was taken The infant was put to the left breast for five minutes No milk had been withdrawn from the right breast

A The right breast is opaque, rounded and bulging

B The left breast is smaller, triangular and less dense, some trabeculae are visible because they are separated from each other due to shrinkage from emptying

subareolar region become larger. The ducts are dilated and varicose They lie close together and their outlines are often indistinguishable The rounded cystlike bodies are seen to increase in

size and number They attain their greatest dimensions about the second day of the puerperium just before the milk comes in When the milk comes in, the ducts are larger and as a rule more distinct Their appearance varies according to the amount of milk in the breast.

Physiologic Alterations during Suckling Propulsion and Emission Serial roentgenograms were used for investigation of the changes

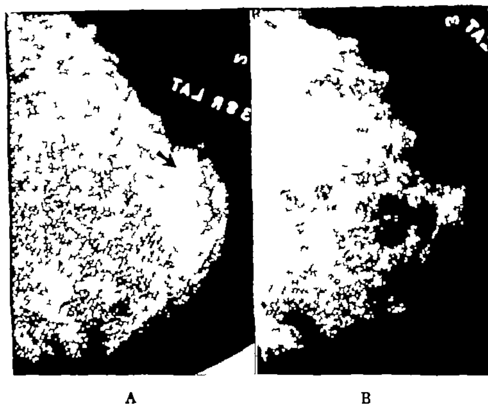


Fig 49 Breast three days postpartum to show dilated ducts and sacculi.

A. The breast is distended with milk, dilated ducts and sacculi are visible in the nipple area (arrows) Note bulging of breast outline around the areola.

B Same breast immediately after nursing The breast is obviously smaller, although, because of its flabby condition, it is spread out and appears larger than it actually is The trabeculae are now far apart, separated by translucent areas Some milk remains in the posterior part of the breast

in the lactiferous ducts during the let-down or "draught" in nursing women. When a nursing mother puts her baby to the breast the infant suckles for a moment, then stops and awaits the "draught" or let-down. Thirty to sixty seconds after nursing has started the mother has a sensation which has been described as resembling both a sneeze and an orgasm. Occasionally it is very





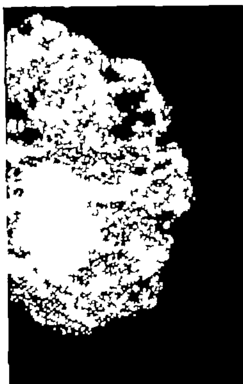
A B

FIG. 50. Series of x-ray films of left breast in the nonpregnant state, during pregnancy and after parturition Multipara, aged thirty-one years.

A. Glandular breast with normal arrangement of trabeculae. There is some haziness in the central part of the breast possibly due to adenosis and a large vein is seen emerging from the area The pale nodule near the nipple is a swollen Montgomery gland.

B The same patient eight and a half months pregnant. Broad digitations typical of pregnancy are seen evenly scattered through the breast. The lactiferous ducts are dilated

painful A few women do not feel it at all As a general rule mothers with abundance of milk are apt to feel pain. In some women milk pours or even spurts from both nipples Occasionally the sensation occurs more than once during suckling Accompanying these sensations there is a characteristic change in shape, or





C FIG 50 D

C. *The same breast nine days postpartum. The patient tried to nurse*, but did not have enough milk. Involution has begun but the breast is still much larger than before parturition. Fluffy ground glass opacities are scattered through the breast but digitations are not distinct. Dilated ducts and small sacculi can be made out in the subareolar area.

D Same breast thirteen and a half months after parturition. Except for a few small fluffy patches the trabeculae are quite distinct. The lactiferous ducts show minimal dilatation—normal for multiparae. The fluffy patches could represent slight adenosis but are probably merely physiologic—the remains of the puerperal state

"ballooning" of the breast in the nipple area. In most women the swelling is below rather than above the nipple and corresponds to the structures involved in the propulsion of milk. Mavis Gunther (1942) notes that "when the breast is being milked by hand, very little milk is obtained unless compression is applied to the ducts subjacent to the nipple at a depth equal to the radius of the areola. It seems that the size of the areola is related to the underlying anatomy" Our own studies confirm this observation.

For studies of the let-down it is imperative that the woman be not disturbed or upset in any way Emotional disturbances in women as well as in cows, and, as Cross (1948, 1954) has recently shown, in rabbits, may interfere with the orderly working of the reflex. The technic was as follows. With the willing cooperation of the mother, a film was taken immediately before nursing Then, without changing the position of the mother or of the x-ray apparatus, the baby was put to the other breast. As soon as the mother felt the draught another film was taken Suckling was then continued on the breast under study until it was emptied as far as possible and a final film was made

In films of nursing mothers taken just before the let-down, the over-all increase in size of the breast is obvious The breast is very dense, the density being chiefly in the posterior two-thirds of the organ During the let-down there is an anterior movement of opacity toward the nipple. This is accompanied by obvious increase in the width of the ducts (figs. 51, 52, 53) Rounded opacities in the subareolar region enlarge and appear as "cystlike" densities (figs. 49, 54) After suckling, the density of the breast has diminished and the organ is considerably smaller, the lactiferous ducts are greatly reduced in size and many of the cystlike structures have collapsed (fig 49B)

Study of our films shows that the subareolar structures undergoing the changes described above are situated anatomically in the same region as the cisterns of animals Cisterns are large cavernous structures which lie beneath the ampullae of the nipple and are a prominent feature of the udders of cows and goats. In veterinary

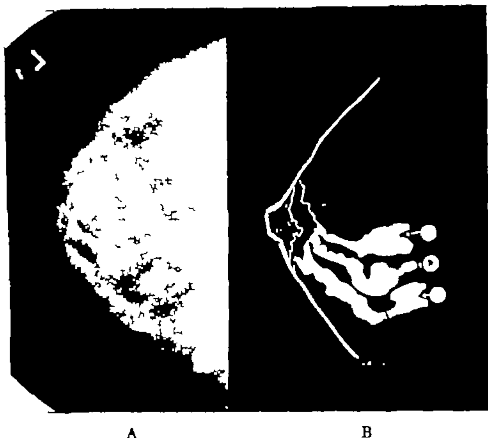


FIG 51 C 1147 Breast immediately before nursing Age twenty five years Multipara, two months postpartum.

A. The breast is distended. The posterior three-quarters of the gland are occupied by more or less confluent fluffy opacities. They represent groups of lobules distended by secretion. Dilated ducts can be seen issuing from them and running to the nipple.

B Three of the most prominent ducts traced from the x ray film have been marked a," "b and c. The outline of the breast although visible on the film, does not appear in the reproduction. It has been traced in the drawing

Duct a" issues from a crenated structure which represents a group of dilated ducts, i.e., a cistern, rather than lobules At first duct a" is quite narrow For the remainder of its course duct a is wide and rather irregular Duct 'b issues from a lobular mass and is probably also connected with another cluster of lobules posterior to the first. Beyond the lobules the duct has a slightly beaded appearance. Tiny round opacities are seen along its course. It ends behind the fibrous pad immediately subjacent to the nipple Duct "c" is narrow Its outline is difficult to see because of two large opacities which lie along its course.



FIG. 52 Breast at the moment of the let-down. Same case as fig 51. The rounded opacities described in fig 51 are larger and many other opacities of the same type are discernible. They extend to the fibrous pad under the nipple and have caused bulging of the area. The opacity from which duct "a" emerged is at least twice the size of the same structure in fig 51 The duct itself is overlaid by similar irregular structures and cannot be distinctly traced. The lobular mass from which duct "b" issued is smaller, but the duct itself is more tortuous and a little wider The terminal portion is not seen. Duct "c" is almost hidden by large opacities with which it probably communicates They are continued to the nipple

terminology "cistern" is used for dilated lactiferous ducts, but sometimes also includes diverticuli which end blindly. Cisterns were never observed in women because until roentgenography there was no appropriate technic for doing so.

Koenecke in 1934 dissected the breast of a woman who had died immediately after parturition. She demonstrated two types of ducts One group, occupying the periphery of the subareolar area developed lobules in the ordinary way The central group gave rise to branches by means of fingerlike processes of the ducts to the third and fourth order without terminating in lobules Near the base of the breast the central ducts were joined by others coming from the lobules situated at the periphery This arrangement of ducts and lobules has been confirmed by us many times in our studies of slicer sections of nonpregnant breasts and in early pregnancy Their fingerlike pattern recalls that of the adolescent

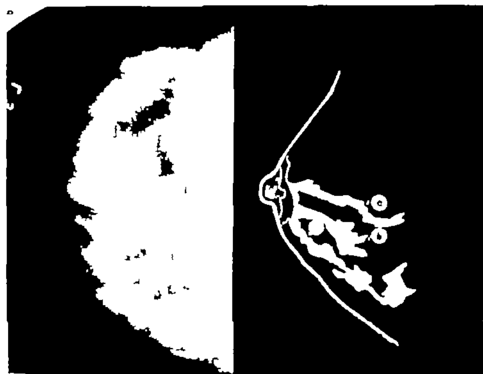


FIG. 53 Breast after nursing Same case as figs 51 and 52. The breast is much smaller The mammary parenchyma has receded and is no longer as dense. Duct "a" is now straight. The opacities which overlaid it are much smaller Duct "b" is clearly visible. It is narrow and straight. The opacities which overlaid duct "c" have almost disappeared. The duct itself is straight and wider than in fig 51



FIG 54 Lactating breast to show distended sacculi at the moment of the let-down X-ray film shows a number of "cystlike" rounded opacities in the subareolar area. These structures correspond to the "sacculi" of Middendorp.

A′. Drawing from x-ray film to show location and size of the sacculi.





FIG 55 A

breast. These ducts grow during pregnancy, but never develop lobules In fact, apart from cases of hyperplasia, no lobules are seen in the area immediately subjacent to the nipple at any stage of breast development (fig 55) Middendorp (1887) had already described somewhat similar structures and named them "sacculi.'



B

Fig 55 Nonpregnant breast. Nipple and subareolar region. Age forty-seven years.

A. Note absence of lobules in central area. One of the lactiferous ducts is dilated. Slicer section.

B Same case as above. Enlarged photomacrograph of section next in series to A. Four of the Middendorp-Koenecke sacculi are visible (arrows)

It would seem that sacculi are the result of expansion of the blind-ending ducts described by Koenecke. It has to be remembered that in anatomical preparations the structures are collapsed and this is even more true of sacculi than of ducts. They would easily be overlooked unless they had been distended by some method of injection before fixation.

In the nonpregnant breast the sacculi are too small to be discerned on the x-ray film, but we have been able to trace the development of opacities through the later stages of pregnancy into their final form. The identification of the structures described by Middendorp with the bodies seen on our films would therefore seem justified, and this view is reinforced by certain functional considerations.

Hormone Mechanisms in Lactation. For a full account of the stimuli concerned in the initiation and the maintenance of lactation the reader is referred to the work of S. J Folley and others. Only the briefest summary will be given here The instigators of mammary growth are estrogen and progesterone. In many species functionally normal lobules develop without ovarian progesterone although its secretion from the adrenal cannot be completely excluded. Both hormones are controlled by the anterior pituitary.

Distinction should be made between lactogenesis (initiation of lactation), galactopoiesis (the maintenance of already established lactation), and the propulsion and ejection of milk Prolactin from the anterior pituitary has long been regarded as essential for the initiation of lactation. The mammary gland responds to prolactin injected intraductally in the intact animal At the same time prolactin has other and quite different effects such as growth and secretion in the pigeon's crop and luteinization of the ovary in hypophysectomized animals. Moreover, it does not act on the breast in the absence of ACTH This implies the existence of an adrenergic as well as pituitary factor A neurogenic factor involving a hypothalamic-pituitary pathway may also be postulated. It is known that growth and secretion of the mammary gland are influenced by neurogenic stimuli. Copious lactation, suffi-

cient to raise several litters was initiated in rats by suckling With certain primitive tribes it is customary to give a motherless baby to the nearest female relative regardless of her marital or puerperal state. In most cases milk secretion is induced in the foster mother by the infant's suckling and the child is successfully reared. We read of an unmarried young woman who put a motherless infant to her breast and produced enough milk to raise the child. This story was long thought apocryphal, but it may well have been true.

The distinction between galactopoiesis and lactogenesis was first realized when Folley and Young discovered that purified prolactin did not increase milk output either in women or in cows, but this could be achieved in cows by injection of diabetogenic extracts of anterior pituitary Purified growth hormone is diabetogenic in cats and galactopoietic in cows To quote from Folley "There is an analogy between growth and milk production in that both processes require a special type of metabolic control involving a restraint of oxidation of metabolites which would otherwise be oxidized in an animal in equilibrium, a metabolic feature common also to diabetogenesis"

Propulsion or the transference of milk from acini to lactiferous ducts is brought about by contraction of myoepithelial cells (Richardson, Linzell) To prove this Linzell performed some interesting experiments in breasts of lactating mice observed under the dissecting microscope. Minimal direct electrical stimulation caused contraction of four or five alveoli. Similar effects over a larger area were obtained by dropping minute quantities of oxytocin, acetylcholine, and some other drugs directly over the acini. The local application of adrenalin had no effect. Since there is no smooth muscle around the alveoli, contraction must have been effected by the myoepithelial cells More recently the same author has observed that in mice, if suckling does not take place, the milk instead of being ejected at the nipple flows back into the prelobular ducts and even into the acini The inference would seem justified that although both propulsion and ejection are normally triggered by oxytocin from the posterior pituitary, the

mechanism of ejection differs in some way from that of propulsion.

Emission or ejection is the process whereby milk travels from the subareolar area to the exterior via the nipple. How this might be effected is suggested by the arrangement which obtains in cows. The cow has a well-designed apparatus for preventing emission of milk from the udder except at milking time. The streak canal or papillary duct presents three, four, or five rounded projections (Furstenberg's rosette) which touch each other, leaving only a star-shaped slit. In addition, folds of mucosa are found at the entrance to the teat canal. When pressure is applied to the teat, the canal shortens. The teat cistern, corresponding to the ampulla in women, balloons out, the rosette is flattened, and the folds disappear so that they no longer interfere with the escape of milk. The mechanism has not been investigated in women, but folds similar to those in the cow certainly exist.

Nagel (1942) made detailed investigation of the musculoelastic structures of the nipple and areola in women. He describes a meshwork of musculoelastic fibers lying immediately beneath the skin The elastic fibrils are intimately connected with the smooth muscle cells and anchor them to the epidermis. The entire apparatus is cone-shaped. The apex of the cone is situated at the tip of the nipple, the broadened base extends to the edge of the areola. Contraction of the muscle causes elongation of the nipple and also exerts a pull on the skin immediately adjacent to the areola The lactiferous ducts within the nipple are not attached to the musculoelastic mesh, but are free to move within it Muscular contraction at the apex of the nipple closes the orifice of the ducts. Suction by the nursing infant holds the canals open. Nagel believes that the pad at the base of the nipple which consists of muscle, elastic, and collagen fibers acts as a sphincter He describes the network of venous channels situated beneath the skin at the apex of the nipple and supposes that it serves as an erectile mechanism and also protects the ducts during suckling. According to Nagel the musculoelastic system of the nipple subserves two functions. (a) erection of the nipple and (b) emptying of the

mammary gland. The erectile function is not in doubt, but the emptying of the gland is a more complicated matter We now know that propulsion is the work of the myoepithelial cells, but emission or ejection may well be the specialized task of the musculoelastic system

Suckling or milking stimulates the ejection of milk. Tactile stimulation of the uterine cervix and electrical stimulation of the central vagus have a similar effect. Emotional disturbances interfere with the stimulus This points to a neural mechanism. Electrical stimulation of the hypothalamus or of the posterior pituitary stalk causes a similar ejection response, but there is also a humoral link. Although lesions in the supraoptic hypophyseal tracts in rabbits prevent the young from obtaining milk, the litter can obtain milk if posterior pituitary extract is injected intravenously Moreover a denervated udder responds to minute doses of oxytocin from the posterior pituitary Anatomic studies by Pallot (1925) confirm the existence of secretory cells in the hypothalamus and show how the secretion may travel by way of the infundibulum to the pituitary portal vessels

Further elucidation of the mechanism of milk ejection is afforded by the experiments of Cross and Harris (1952) They showed that the hypothalamus through its connection with the posterior pituitary gland has a controlling function in the milk ejection reflex. More recently Cross (1954, 1955) has mapped out the milk ejection response obtained by stimulation of different sites in the hypothalamus of lactating rabbits Stimulation of the supraoptico-hypophyseal tract gave rise to milk ejection from the cannulated teats of lactating rabbits But after ejection had been excited by administration of oxytocin, similar electric stimuli applied to the dorsal, lateral, and posterior areas of the hypothalamus caused inhibition of the reflex. The peripheral inhibitory path was via the sympathetic. Inhibition was brought about either directly by stimulation of sympathetic nerves, or less effectively, by splanchnic stimulation or by injection of adrenalin. Vasoconstriction within the mammary gland was the factor responsible

for the nonejection of milk, but as Linzell has shown, vasoconstriction does not interfere with stimuli applied directly to the gland. During inhibition the young were unable to remove milk from the mammary gland by suckling This again suggests a separate mechanism for emission or ejection. In a subsequent paper Cross studied the effects of emotional disturbance on milk ejection in rabbits. He concluded that "while sympathetico-adrenal activation does occur, the main factor in emotional disturbance of the milk ejection reflex is a partial or complete inhibition of oxytocin release from the posterior pituitary gland "

Cross's experiments confirm the essential role of the posterior pituitary hormone in milk ejection, but they do not explain the precise function of the subareolar structures.

In women the subareolar region is an area with a radius corresponding to that of the areola When suckling, the infant grasps the areola together with the nipple and the rhythmic movements of the jaws are directed toward emptying this part of the breast. Depleted channels are refilled from ducts of the second and third order and from the acini. For efficient feeding the lactiferous ducts must be refilled promptly and smoothly and not overfilled. Overfilling results in cessation of milk flow by obstruction at the nipple. Extreme pressure within the lactiferous ducts could prevent the operation of the ejection reflex and may explain the intense prelactation engorgement in the breasts of some women as well as the establishment of the flow which often follows stilbestrol medication

There is little doubt that lactiferous ducts and sacculi in women are the homologues of cisterns in animals. They occupy a similar anatomic situation and behave in the same way. Cisterns have long been thought of as storage spaces Koenecke makes the same suggestion with regard to sacculi. There are several objections to this view. We agree with Folley that in most animals the storage capacity is far too small to be of real significance. In cows the cisterns contain not more than 10 per cent of the milk yield (Turner). The capacity of the lactiferous ducts and sacculi has not

been measured in women, but it is evidently even less in proportion. Furthermore, the idea of storage space does not tally with the pronounced dilatation of lactiferous ducts and cisterns which is observed at the moment of the let-down. In cows and goats Folley (1948) found that injections of posterior pituitary extract just before milking time produced a sharp rise of pressure in the cisterns Judging from anatomic and histologic preparations and from the movement of milk during suckling, it would certainly seem that storage is effected in the smaller ducts and to some extent in the alveoli themselves, and this is also the opinion of Folley

The above considerations suggest that the subareolar region is closely connected with the regulation of pressure. Direct proof is lacking, but the hypothesis that the sacculi provide the trigger mechanism for even filling of the lactiferous ducts is an attractive one and is supported by Whittlestone s investigations

Whittlestone (1954) conducted experiments on intramammary pressure changes in the lactating sow Milk ejection followed injection of oxytocin, but the response was delayed if the experiment was repeated several times during one milking He says "One of the most evident characteristics of the milk-ejection process in the sow is the suddenness with which the pressure rises and falls Attempts to prolong the rise may result in a biphasic response which suggests that after the initial triggering, there is a phase of relaxation and insensitivity to the hormone, followed by further response." The sudden fall in pressure and the biphasic response observed by Whittlestone might well be the result of inhibitory stimuli to the lateral paraventricular regions of the hypothalamus, alternating with excitation of the posterior and supraoptic nuclei.

The nipple itself would seem to be the point of origin for the neurohormonal reflex responsible for propulsion and ejection. In support of this concept are the observations of Hooker and Williams (1941), who found that the application of turpentine to the nipples of rats retarded lactation involution. The explanation would be that emptying of alveoli, due to the action of oxytocin

liberated from the posterior pituitary, stimulates secretion. Concomitantly the pressure would rise in the lactiferous ducts Further evidence of a nipple reflex is provided by Tgetgel (quoted by Turner) who noted a rise of pressure within the udder when the teats of cows were handled.

The path of the reflex for propulsion of milk from alveoli to lactiferous ducts is fairly clear. A stimulus arising in the nipple travels via a neural path to the supraoptic nuclei of the hypothalamus. Thence it is relayed to the neuro-hypophysis. It is not certain whether this link is a direct neural stimulus or whether it is due to secretion from the hypothalamus reaching the posterior pituitary via the pituitary portal plexus. There is at any rate no doubt that oxytocin is released into the blood stream and comes in contact with the myoepithelial cells in the lobules and prelobular ducts Contact is facilitated by the tendency of myoepithelial cells to lie in apposition to capillary walls. The myoid apparatus contracts and milk is propelled into the lactiferous ducts. Distention of these ducts and probably also of the sacculi gives rise to the sensation of the let-down The mechanism for ejection or emission then comes into play. Anatomically, ejection seems to be provided for by contraction of the muscular apparatus of the nipple and areola, but it is unknown whether this is a direct effect of oxytocin or is mediated by some other mechanism depending on distention of lactiferous ducts When distention of ducts and sacculi has reached a certain point an inhibitory reflex comes into play. No proof is available, but it is logical to suppose that specialized structures such as sacculi have a function The hypothesis that their expansion sets in motion an impulse which reaches the inhibitory centers in the hypothalamus is an attractive one. The rest of the pathway has been worked out by Cross. The end point is constriction of the arterioles supplying the mammary parenchyma following stimulation of the sympathetic fibers. Cross suggests that the intense vasoconstriction produced by adrenalin acts by preventing the access of oxytocin to the myoepithelial cells. This view is reinforced by Linzell, who showed that direct applica-

tion of oxytocin to the cells following adrenalin is still effective in producing contraction A glance at fig 25 shows how the anatomic arrangement of vessels around lobules and smaller ducts bears out Cross s hypothesis Constriction of the anastomosing arteriolar ring would practically cut off the capillary blood supply to the myoepithelial cells Since the sensation of let-down and its accompanying maximal distention occurs only once in most women, it is probable that subsequent inhibitory reflexes are focal rather than general and affect only limited areas in the breast An even flow of milk to the nursing infant would thus be ensured

Lactation Involution In lactation involution, as in other phases of the normal breast, there is no even, regular regression toward the nonpuerperal condition. Some acini will continue to secrete for long periods, others undergo rapid involution.

For a few hours after parturition the breast is flabby It would seem that if stilbestrol is given at this time secretion is arrested (fig. 57), but we have no histologic confirmation of this

When the milk comes in, usually two to six days after delivery, large fat-containing globules appear in the acinar cells, and signs of lactation such as secretion with colostrum cells are found in the alveoli even if the patient has not nursed Figure 56 is from a hypertensive woman who died of intracranial hemorrhage four days after Cesarean section. Vacuolated epithelial cells are seen in the illustration as well as several nuclei belonging to myoethelial cells Another specimen of about the same puerperal date showed similar features There were no signs of involution in either of these breasts, but early involutional changes were evident in a young woman who died of congenital heart disease seven days after delivery Her breasts were poorly developed. The lobules were small Most of the acini contained some secretion, although they were seldom distended The fibers of the myoepithelium were broadened and had a somewhat glassy appearance. They filled the widened spaces between the acini. In some places groups of small acini were seen, these had a shrunken appearance They contained little or no secretion and a lumen was sometimes hard to

see. The myoid cells around the shrunken acini were also small and their nuclei were pycnotic.

Another specimen of about the same puerperal date was obtained from a woman who received a blow in the abdomen and died of peritonitis following delivery of a stillborn eight-months fetus. The lobules were well developed and many of the acinar cells presented large vacuoles Other acini were contracted. Some were represented by clusters of small, rather deeply staining cells resembling those seen in a later stage of involution. Myoethelial cells and fibers were everywhere in evidence and followed the usual

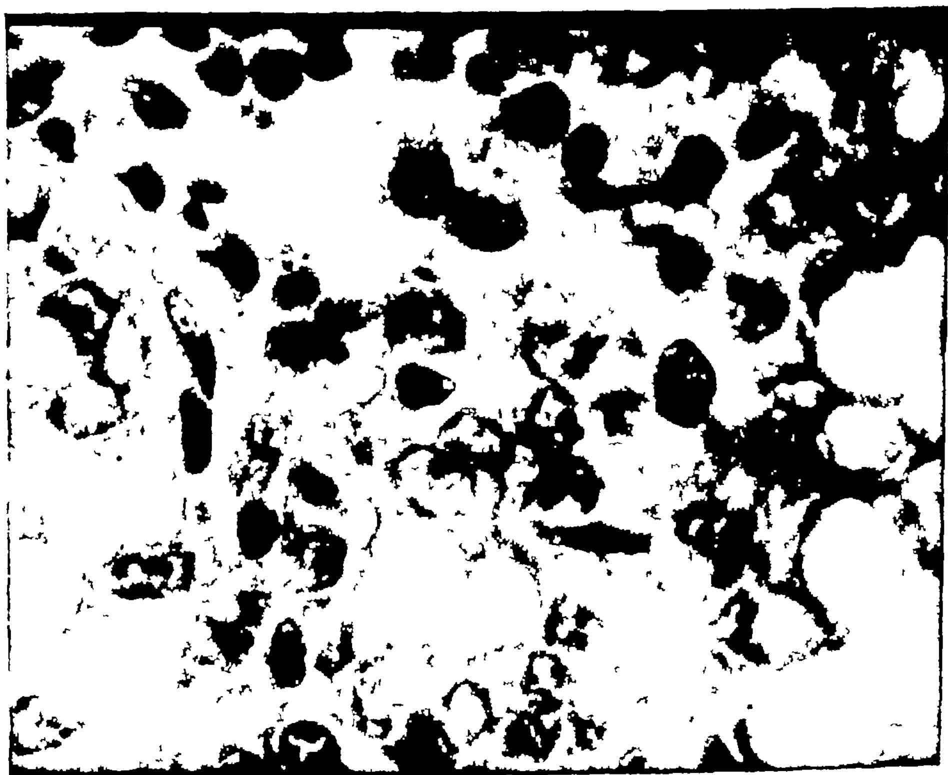


FIG. 56 Eight months pregnancy Age twenty-six years. Delivered by Cesarean section Died four days later of ruptured cerebral aneurism, never nursed Paraffin section shows various stages of myoid development There are several embryonic nuclei. Some cells show early branching of the cytoplasm. On the left are two mature myoepithelial cells.

pattern. The smaller the acini, the more closely packed were the myoid nuclei and the more distinct the fibers The broadest fibers showed a tendency toward hyalinization.

A specimen of breast, which may be considered normal in a woman of twenty-three years of age, came to us as the result of an operation for fibroadenoma forty-nine days after delivery and twenty-five days after nursing was stopped (fig 124) Two fibroadenomas lying close together were actively lactating This could be expected since it is characteristic of fibroadenomas to lag behind in the changes that are affecting the rest of the breast. The adjoining breast showed all varieties of lactation involution. Some lobules resembled those seen in many cases of adenosis and would hardly have suggested lactation involution These were marked by hyperplasia of the basal cells, many of which showed early differentiation to myothelium A considerable proportion were vacuolated and appeared about to degenerate. Some ductules contained a little secretion, others were collapsed. Between the ductules, myoid cells and fibers were numerous Other lobules showed dilated acini surrounded by a jumble of nuclei belonging partly to degenerated acinar cells, partly to the myoid Elsewhere there was periacinar fibrosis due to myoid proliferation. In fact, two processes seemed to be at work (a) degeneration of cells lining the acini, whether epithelial, basal, or myothelial, and (b) proliferation and differentiation of myoid cells to form fibrous tissue. All the cell nuclei were small compared to those of the pregnant or actively functioning breast. Occasional examples of atrophied ductules were found, consisting of a few shrunken deeply staining epithelial cells, surrounded by a zone of hyalinized myoid The antithesis of this was seen in one group of acini which were indistinguishable from those of normal lactation. The larger ducts were moderately dilated, although less so than in actively lactating breasts The fibroadenoma showed ducts of the usual distorted pattern, but much more dilated than usual They poured milky fluid when the tumor was sectioned in the fresh condition. The ducts were intermingled with groups of dilated acini lined by



FIG. 57. C 1177 Lactation involution due to stilbestrol Primipara, age seventeen years, two days postpartum. Although some colostrum remains in the lactiferous ducts, the subareolar area is no longer bulging and rounded as it is during lactation This is an immature breast which has developed during pregnancy (*Cf* with figs. 43 and 15.)

secretory epithelium. The myoid fibers around the most active acini were similar to those of the pregnant breast, but toward the edge of the "lobules" where the acini were smaller and farther apart, the fibers became broad and hyalinized. They merged insensibly with the intraductal tissue of the tumor

In contrast to this case were two women, both of whom died of tuberculosis, one nineteen days, the other nine weeks after giving birth to healthy babies The breasts of both presented extreme uniformity of lobular involution. Uniformity of architecture due to generalized atrophy is characteristic of any breast in tuberculosis The first patient, aged twenty two, showed well-developed lobules, but the acini were uniformly small Only a few contained secretion. The myothelial fibers were broad, refractile, and remarkably distinct. Occasionally the myoid surrounding the alveoli was definitely hyalinized The nuclei were fairly abundant and small, with rounded or pointed ends In the second case the lobules were also remarkably alike and much more atrophic than in the previous specimen. No new lobules were being formed The ducts were somewhat dilated, a characteristic of pregnancy The lobular atrophy was exaggerated and was partly due to tuberculosis The acini were minute and surrounded by a dense feltwork of small myoid cells with large numbers of pointed nuclei and fine, rather short fibrils

An example of a late stage of postpartum involution was from a woman aged twenty-four years who was delivered of an eight-months stillborn fetus three months before her death from cerebral abscess The breast sections presented a collection of rather large lobules which at first glance suggested some form of nonpuerperal hyperplasia. However, close examination showed that the acini were lined by one layer of irregular, rather small cells, which were not always contiguous The irregularity of the cells was not due to autolysis since the autopsy was performed four hours after death. Most of the alveoli were slightly dilated, but very few contained secretion. Small myoid nuclei lay along the basement membrane which was formed by their fibrils Branching myoid cells

were found between the alveoli and occasionally lay between the epithelial cells. The prelobular ducts were slightly dilated and surrounded by fine fibrils of myoid origin. In another place, there were scattered small lobules in which the acinar epithelium appeared normal The myoid was perhaps a little more in evidence than usual, but there was no real difference between these lobules and those of the nonpregnant normal breast They could have been newly formed lobules, indicating resumption of the menstrual cycle.

Roentgenography of Lactation Involution In our series the earliest signs of involution were noted in a young primipara who was given stilbestrol immediately after parturition (fig. 57) Dilatation of lactiferous ducts was still present, but there was not the same distention of the subareolar area as takes place under the stimulus of suckling (figs 49, 52, 54). The x-ray film shows that the ducts and sacculi are less crowded The sacculi are small and are probably only visible because they are not masked by overdistended ducts Following this stage x-ray films show rapid narrowing of the lactiferous ducts. They are no longer tortuous, they decrease in size until involution is complete, but slight dilatation often persists and may be considered normal for the multiparous breast. Sacculi are no longer discernible on the x-ray film although their counterparts can be seen microscopically as the clusters of blind-ending ducts already described (fig 55) With cessation of secretion the lobules shrink, the breast becomes less dense and trabeculae reappear. In some cases, especially in postlactation involution, the film shows a generalized haziness due to loss of architecture through the breaking up of the lobules, infiltration by phagocytic cells, and edema As involution proceeds irregular scattered opacities are seen resembling those of adenosis (figs 46B, 50). These finally disappear and the breast resumes its normal pattern

In women who have not nursed involution takes place in about two to three months Judging from cases under our observation the process would seem to take longer and is more irregular once

lactation has been established Irregular involution may be expected in cases where drying up of the secretion is accompanied by pain and when nursing has been stopped on account of a breast lesion. Any form of hormone imbalance may interfere with the normal process, but x-ray films taken before pregnancy and after involution show that in the absence of fresh hormone disturbance the breast reverts to its former type. In the case illustrated by fig 50 we were able to compare films taken three months before pregnancy, at eight and a half months gestation, nine days postpartum, and thirteen and a half months postpartum. Her first admission was for operation on a recurrent mass in the right breast due to adenosis (fig 91) The last film, more than a year after postpartum involution, shows a normal multiparous breast.

THE POSTMENOPAUSAL BREAST

The normal postmenopausal breast is characterized by gradual involution of lobules and relative increase in the fibrous tissue of the trabeculae. In the majority of women, as the parenchyma diminishes, the adipose tissue is increased. The breast becomes flabby, but the total volume may remain the same or be increased or diminished, depending on the nutritional state of the individual. Intertrabecular fat is sometimes lacking and even the subcutaneous fat may be almost absent in very thin subjects The breasts then present a firm compact core of mammary tissue in contradistinction to the flabbiness of fat-containing organs A proportion of postmenopausal glands exhibit fine nodularity, most commonly in the upper and central parts of the breast Although frequently found, this type of fibrosis is strictly not a normal condition, but follows certain dysplasias

As age advances, the parenchyma becomes more and more atrophied and the trabeculae become correspondingly thinner (figs 59, 60) The fibrous core in nonfatty breasts diminishes in size. But the nodular fibrosis mentioned above remains more or less unchanged.

Anatomically, the over-all appearance of the breast corresponds

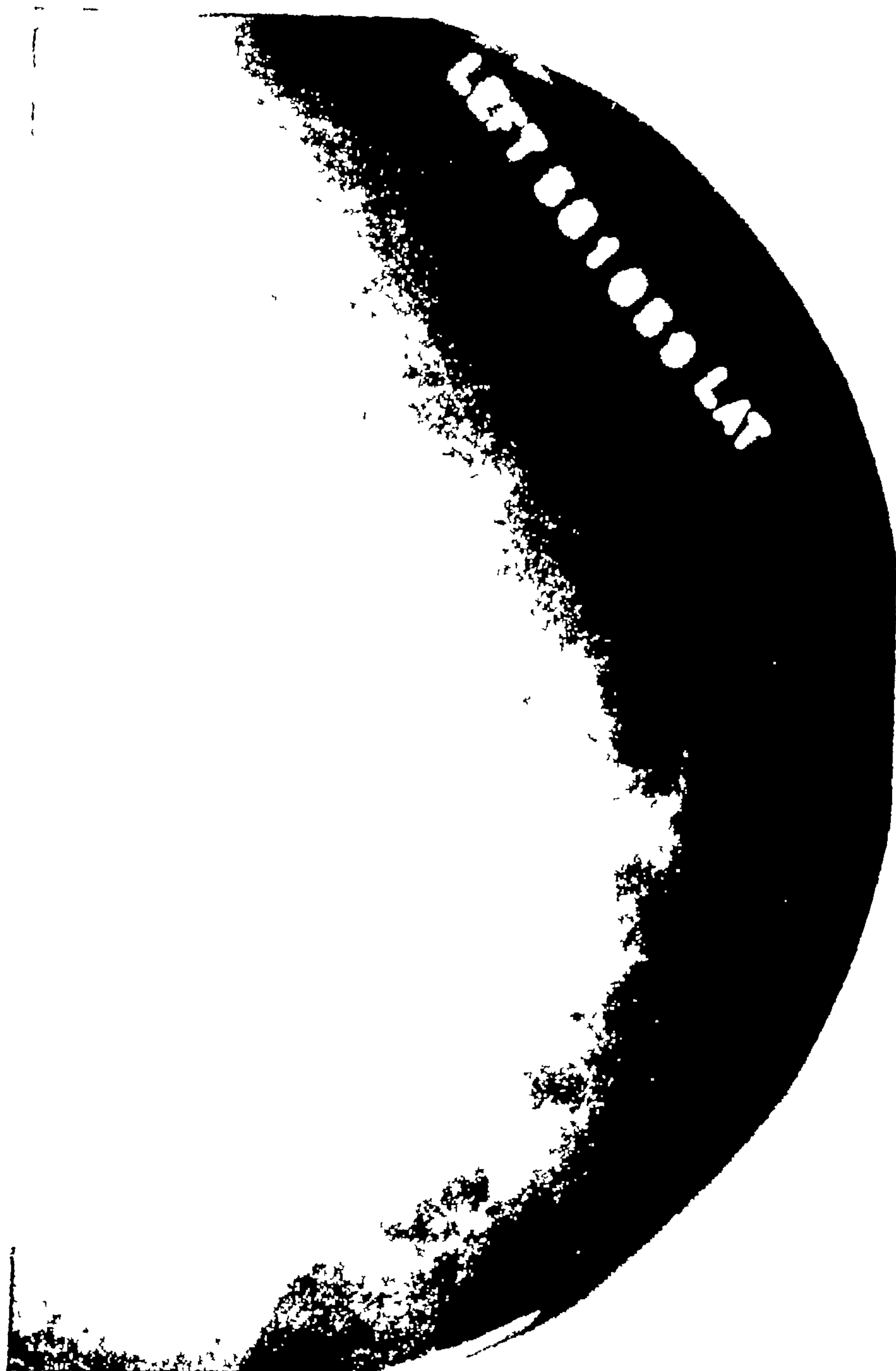


FIG. 58 Involutional fibrosis—congenital inversion of nipple. Age fifty-six years Asymptomatic The breast trabeculae are considerably thinner than in the glandular type of breast. The amount of fat is increased. Here and there are small irregular patches representing

with the degree of atrophy or hyperplasia. There are many variations In general, the ducts shrink and the lobules are reduced to a few atrophied ductules Lobules are most numerous at the base, but are also scattered in the trabeculae where fibrous tissue predominates Some of the more fibrous breasts show hardly any



FIG 59 C 961 Atrophy following involutional fibrosis Age sixty-six years. Note attenuated fibrous trabeculae. Vessels show a few patches of calcification. The white streaks below the nipple are due to vascular calcification.



FIG 60 C 1542 Lipoma in an atrophic breast. Age seventy years Patient presented a soft, discrete mass 3 cm in diameter medial to the nipple X-ray films (cephalocaudad view) show slight displacement of the breast trabeculae by a radiolucent mass (arrows) The breast is atrophic in type. Pathology: Lipoma.

lobules but contain slightly dilated ducts with a pattern resembling that of the adolescent.

Microscopically, the epithelial cells lining the ducts are smaller and the nuclei stain deeply The myoepithelium, on the other hand, is usually hyperplastic, as was pointed out in 1939 by Günther Some of Günther's sections may have been from carcinomatous breasts where myoid hyperplasia is to be looked for, even in young women. But in elderly women in general the myoepithelium tends to be prominent and this is consistent with what might be expected theoretically The growth and development of the myoid cells contribute to the fibrosis

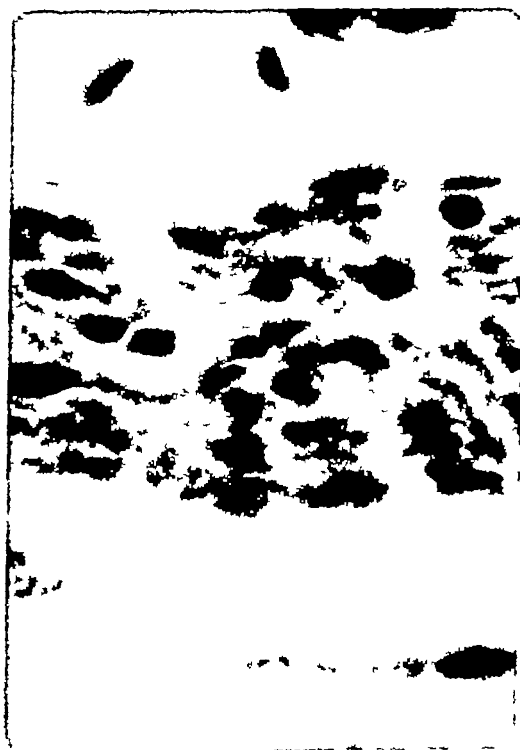
Lobules in postmenopausal breasts are by no means always stationary Proliferation and involution take place in them Occasional ducts are found filled with proliferating glandlike structures The process of involution differs from that seen in the normal sexual cycle, but similar changes occur not infrequently in the glands of younger women with mammary dysplasia.

The sequence of events is noted chiefly in small groups of ductules and in the prelobular ducts and is easy to follow when the Masson-Goldner trichrome method is used The first alteration noted is the appearance of red-staining deposits in the cytoplasm of the basal or myoepithelial cells of the peripheral part of a lobule (fig 61) The central intralobular duct may remain intact or be affected later The cells in which the red deposits appear are vacuolated. The nucleus loses its chromatin pattern and takes on a uniformly dark stain with hematoxylin It becomes pycnotic, shrinks, and disappears The cell outlines become blurred. At this stage masses of red hyalin material are seen, together with large vacuoles and remains of nuclei Often the epithelial cells are shed into the lumen of the duct which may be dilated Otherwise they follow the same process of hyalinization. If the central duct has degenerated later than the peripheral ducts, the next stage shows a circumscribed area of smooth structureless material. In the center of this degenerated mass, nuclei derived from the central duct can still be seen. Finally, the products of degeneration form a





A FIG 61. B



nodule which becomes gradually indistinguishable from the adjacent connective tissue. If on the other hand the central duct is not destroyed, it may become surrounded by a hyaline band as in mammary dysplasia.

The roentgenographic picture of the postmenopausal breast is characteristic. Normal involutional fibrosis shows the trabeculae forming a strandlike pattern on a relatively clear background (fig 58) These strands run from the base of the breast to the nipple and are narrower and more sharply outlined than in the actively functioning gland. They may be interspersed with occasional irregular opacities These are most likely due to limited patches of fibrosis, possibly the result of a postmenopausal hyperplasia. When fat is absent the trabeculae lie close together On the film they are seen as a dense opacity in which individual structures cannot be recognized The x-ray film of nodular glands presents a quite different and highly characteristic picture. A complete description of this hyperplastic fibrosis will be given in the discussion of the dysplasias and carcinoma.

FIG 61 C 1339. Stages of noncyclic involution in breast ductules. Age sixty years. For about thirty years the patient had multiple nodules in both breasts Their location was not constant. They usually appeared in the premenstrual phase and disappeared with the onset of the period. After the menopause a few small masses were felt. They varied in size and often disappeared completely

A. Small duct with remains of two ductules close to the wall. The epithelial cells are large. The cytoplasm is vacuolated. Globules are seen in the duct on the surface of the cells. Centrally there is inspissated protein secretion. The degenerating ductules show partly hyalinized cells, chiefly myoepithelial.

B Small duct. The epithelium is in process of disintegration. The lumen contains inspissated protein secretion surrounded by debris At the periphery are myoepithelial cells undergoing hyalin degeneration.

C. A later stage of degeneration. Ductule sectioned longitudinally shows remains of epithelial nuclei surrounded by partly hyalinized myoid.

CONGENITAL ANOMALIES OF THE BREAST

Accessory Breasts. Supernumerary mammary organs or rudiments are very common They are said to be rather more frequent in the male than in the female, but with the advent of roentgenologic diagnosis this order may well be reversed. They are generally found along the milk line, but have been recorded on the cheek, neck, ear, trunk, upper arm, and thigh. It is unusual to find a complete breast, i.e , one containing nipple, areola, gland tissue and fat (fig 62). More often one or more of these elements are lacking. Multiple nipples may be present, or merely "polythelia pilosa" when only a patch of hair is seen.



FIG. 62 C 1198 Axillary breasts. The patient, aged thirty years, had bilateral axillary breasts with nipples, and supernumerary nipple below each breast The outline of a breast with a well-formed nipple (n) is seen in the left axilla Breast tissue is present in the right axilla, but the nipple was not taken in profile and is therefore not seen. Symptoms occurred following a five-month course of estrogens

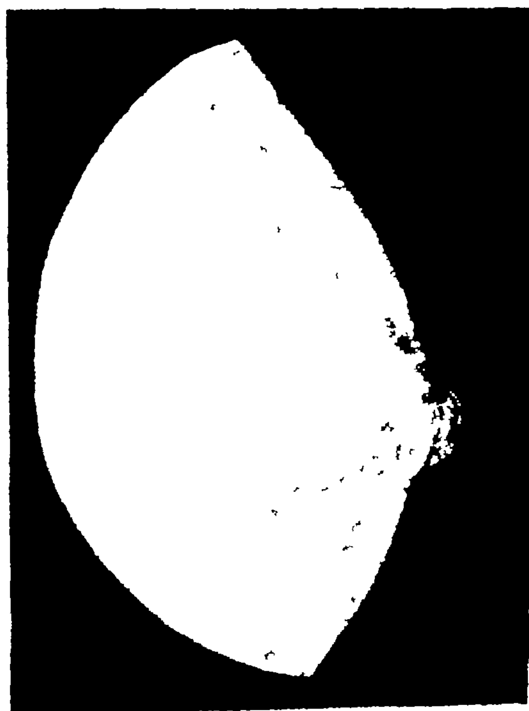
The majority of accessory breasts in women occur in the axillae where they are nearly always bilateral, the nipple and areola are usually absent. When palpated, axillary breasts may be mistaken for an extension of mammary tissue into the axilla, and since many are asymptomatic the diagnosis is unlikely to be made Approximately 1 per cent of the patients in our series had symptoms referred to one or both axillary breasts Many women notice these breasts first during pregnancy When there is a nipple, lactation ensues In most cases there is no exit for the secretion, and involution of the glandular tissue takes place soon after



FIG 63 C 1129 Axillary breast. Age forty two years Slicer section shows scanty, poorly developed lobules Most of the terminal ducts are dilated.



FIG 64



A′

parturition. In nonpregnant women, with the exception of one girl of eighteen years, the average age of onset of symptoms was forty years The symptoms are those of adenosis in general The patient complains of a tender mass, worse before periods The swelling is usually increased premenstrually and sometimes disappears postmenstrually Some women complain only of a "drawing feeling' In our experience all axillary breasts removed at operation showed adenosis or mazoplasia (fig 63) It would therefore appear that symptoms are due to dysplasia rather than to the existence of an accessory mammary gland

Recognition on the x-ray film is easy once the possibility of the anomaly is borne in mind Apart from its position, the accessory organ may betray itself by its shape and by a line of demarcation between it and the normal gland (fig 62) The trabeculae, instead of following the line of the breast proper, converge to a point which corresponds to the prenipple area. Theoretically an axillary breast could become the seat of carcinoma, but since the growth when discovered has disrupted the tissue we have no means at present of ascertaining how often the complication actually occurs

Anomalies of Nipple and Lactiferous Ducts Deformities of the nipple may be congenital Inversion of the apex or, less commonly, retraction of the entire nipple may be present. Often the nipple is flat and fails to evert sufficiently to enable the infant to suckle. Occasionally a nipple is split in two or more segments with a duct opening at the apex of each.

FIG 64. Malformation of lactiferous ducts Colored woman aged thirty four years She had nine children, but in spite of repeated efforts, had never been able to nurse for more than a few days (see text) X ray film of the anterior part of the left breast two days after parturition shows a large beaded duct (arrow) entering the fibromuscular pad beneath the nipple. Below the larger duct, two smaller ones join the main channel before it enters the fibromuscular pad. The pad itself and details of the nipple cannot be seen on the reproduction. The mammary parenchyma is extremely scanty for the puerperal state. The breast would fall in Engel s Class 2

A Drawing of x ray film.



FIG 65. Lactiferous ducts opening on areola Age thirty-three years After a pregnancy, three years before, patient was unable to nurse because the milk spurted in the child's face. X-ray film· Three

A variable number of ducts, put by most authors at fifteen to twenty, normally open onto the nipple. A lesser number may be present. Occasionally they are reduced to a single duct. We were able to examine one such case soon after parturition (fig 64) The patient, a colored woman of thirty-four years, had nine children. She wished to nurse them, but had never been able to do so The breasts did not increase in size during her pregnancies and within a few days they became flabby and ceased to secrete. Daily clinical examinations after parturition showed remarkably flabby breasts, with relatively little glandular tissue. The nipples were prominent, but the areolae were very small. One large opening was seen at the bottom of a cuplike depression in the center of each nipple. The right nipple showed a small duct opening on the edge of the



FIG 65 A

groups of lactiferous ducts are seen in the subareolar area. Instead of converging at the nipple they diverge and open on the areola.

A Drawing from x ray film.

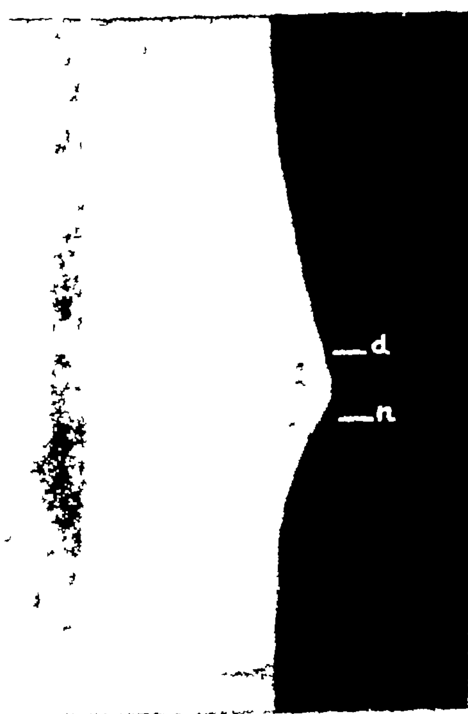


A



B

FIG. 66



A'

cup Seven days after parturition the milk failed in spite of the mother's efforts to continue nursing The x-ray films showed only one large lactiferous duct entering the fibromuscular pad. The breast parenchyma was extremely scanty

Occasionally ducts open on the areola as well as on the nipple (figs 65, 66) In a few of our cases the ducts opened on the surrounding skin, after the manner of the duck-billed platypus One patient, aged twenty years, had noted nothing abnormal until pregnancy when the ducts discharged serous fluid. She was not allowed to nurse, but discharge continued for about seven months after parturition. The area was then excised. The ducts arose from a group of normal lobules situated superficially Discharge from the areola was discovered in three girls aged thirteen, fourteen, and ten years, respectively In the first a dilated duct was excised beneath the areola in each breast. Films from this case taken two years later, when the breasts were fully developed, showed ducts ending beneath the areola. In the second girl the condition cleared up spontaneously The third child had precocious development of the mammary glands Following a blow, a bloody discharge from an opening on the right areola first called attention to the condition Openings were present lateral to the nipple in both areolae (fig. 66) Three months later the openings were closed and could no longer be discerned A similar condition occurred in an adult aged thirty three years After parturition the ducts opened up and milk spurted over the child's face when she attempted to nurse (fig 65)

FIG 66 Precocious development with lactiferous ducts opening on areola in girl of ten years.

A and B X ray films of left (A) and right (B) breasts The breasts show precocious development. The ducts are dilated. Some end at the areola and do not enter the nipple.

A Drawing from x ray film of right breast to show duct entering areola at "d."

PART II

The Dysplasias

The Dysplasias

HISTORY AND CLASSIFICATION

MAMMARY DYSPLASIA is a general term embracing benign lesions peculiar to the breast and essentially due to hormone disturbance. Noncancerous tumors of the breast were noted by Galen (A.D 131–201) In more recent times Bellini (1730) wrote on benign mammary tumors In the last century Colles (1811) gave the first clear clinical description of dysplasia He noted its connection with irregular menstruation and the disappearance of the tumors after pregnancy Sir Astley Cooper (1831) in his classic volume *Diseases of the Breast* speaks of "hydatiform' cysts In his *Anatomy of the Breast* he describes changes in the feel of the breast brought about during the menstrual cycle. Benjamin Brodie (1846) laid a solid clinical and pathologic foundation for what he named "sero-cystic" disease. His observations were repeated by Reclus (1883) Histological observations were added by Schimmelbusch (1892) Prominent in the early part of the century are the names of Aschoff, Semb, and Cheatle. German authors from 1890 onward linked some forms of dysplasia, especially abnormal secretion with pelvic disorders Moszkowicz (1927) noted uterine disorders and alterations in the sexual cycle in cases of mastopathy Ingleby (1932) showed that cyclic changes occurred in fibroadenomas and postulated that these tumors were merely a local manifestation of the generalized disorders common in the mammary gland especially toward the menopause But there was still a long way to go before a correct understanding of mammary dysplasia could be reached. Meanwhile the utmost confusion reigned Each author contributed something, but since he used his own terminology, or like Humpty Dumpty, made existing words mean only what he chose them to mean, confusion became worse confounded. The anatomists, who might have helped, did not know that they held the key to the solution and the majority of pathologists were

unaware that they had lost it. Recently help has come from an unexpected quarter. Our studies of x-ray films of the breast taken in conjunction with serial sections through the entire organ or operation specimen have led to a reclassification of the dysplasias and to a clarification of their underlying pathology.

Pathologically speaking, mammary dysplasia is essentially an abnormal interplay of epi- and myothelium. It has no connection with bacterial inflammation. The term "mastitis" is a misnomer and should be dropped "Fibrocystic disease" is widely used. As a descriptive label it fits many cases, but it offers little or no help in distinguishing between the varieties of dysplasia, a distinction which is often important from the point of view of prognosis Although much has been written on cysts of the breast very little has been said of different types of cysts, and for this reason much of the voluminous work on the relation of cysts to carcinoma is valueless.

Classification of any group of disorders is valuable in so far as it conforms to nosological entities. In other words, a classification must have clinical as well as roentgenographic and pathologic significance It must be capable of being translated into microscopic terms, but it is not microscopic in its inception. There should be a clear clinical implication, not only of diagnosis but also of prognosis and treatment. An attempt must be made to distinguish physiologic aberrations from the strictly pathologic. Breast lesions do not fit into absolute compartments. There is a certain amount of overlap between the physiologic and the pathologic and between the types of dysplasia No system therefore is entirely satisfactory, but so far as cyclic disturbances under the general heading of mammary dysplasia are concerned, we propose the following simple, logical and easily applied classification.

Classification of Mammary Dysplasia

1. Hypertrophy
2. Adenosis
3 Mazoplasia fibrosa

4. Mazoplasia cystica
5. Fibroadenoma
6. Secretory disease
7. Mastopathy (Schimmelbusch's disease)

Intraductal hyperplasia and papilloma, although often hormonal in origin, do not correspond to any normal breast pattern. They are neoplastic rather than dysplastic and are so classified.

Before proceeding to discussion of separate dysplasias it is well to clarify the anatomic and pathologic terms commonly employed. Such words as trabecula, stroma, parenchyma, and lobule are defined in books, but when applied to the breast there is considerable difficulty in knowing just what is meant, a difficulty which most authors do not face squarely. The main confusion has arisen because of failure to grasp that the mammary parenchyma, defined as the essential or functional elements of an organ as distinguished from its stroma or framework, is both epithelial and fibrous and that both epithelial and fibrous elements arise from the same layer of undifferentiated basal cells. Since both parenchyma and stroma are fibrous they are usually impossible to distinguish grossly. Moreover, when a lobule undergoes involution it is replaced by fibrous tissue and it is then indistinguishable from the original stroma. Theoretically it is still part of the parenchyma.

A trabecula, defined as forming an essential part of the stroma, actually consists of both stroma and parenchyma. In practice the two elements cannot be separated either grossly or radiologically. Since the term is sanctioned by usage, "trabecula" is retained. "Lobule" also gives rise to some ambiguity. A lobule is a group of ductules arising from the distal extremity of a duct. It must not be confused with the club-shaped terminal ducts of the adolescent. In the adult, because of hormone imbalance, ducts may only reach the adolescent stage instead of developing into lobules. Or a lobule may begin to develop, but instead of continued subdivision brought about by proliferation at certain growing points, the entire duct wall grows. This results in a collection of cysts, which are

small or large depending on the stage of development reached before the abnormal stimulus intervened and also depending on its intensity. The variability of the process makes it difficult to decide at what point to use the term lobule for these structures.

Although intermediate forms exist, the dysplasias outlined above are fairly stable in that they may continue for several years without alteration in type. Changes in the pattern of dysplasia reflect changes in the hormone balance of the individual In some individuals there is progression to the mixed type—mastopathy Pregnancy and lactation may have a beneficial effect on the disease and after the menopause the lesions often regress.

The possibility of progression of benign dysplasias to a neoplastic state must not be overlooked. At the present time although it is generally accepted that carcinoma occurs four times as often in dysplastic breasts as it does in normal breasts, we have much to learn of the type of dysplasia which precedes the malignant change. Some forms of intraductal hyperplasia may be thought of as precancerous, but this is the only potentially malignant lesion of which we are at all certain. Perhaps the most important objective of classification is the distinction of intrinsically benign from potentially malignant states.

HYPERTROPHY

Hypertrophy is generally used to denote an over-all excessive enlargement of one or both breasts. The enlargement is due to overgrowth of the parenchyma There is often concomitant increase in size from deposits of fat, but this is not hypertrophy The hypertrophied breasts of infants have been described and up to the age of six months should not be thought of as pathologic After this age the infantile type of hypertrophy is rare

Occasionally postnatal hyperplasia persists beyond infancy or regresses to return again months later. A case of this type was seen by us in a twenty-month-old girl. When two months old she had a swelling of the left breast which subsided At twelve months of age the mother again noted a swelling. At times the left breast was

blue and tense. Then it would become smaller and sometimes the swelling disappeared altogether On the whole it had increased in size. There was no tenderness and there had never been any nipple discharge. The right breast was normal. The child was well developed and weighed twenty-six pounds She had never been breast fed. The only etiologic factor that we were able to uncover was that the father had severe diabetes of the pituitary type. Surgery to the breast had been proposed, but fortunately the physician in charge preferred to send her for an x-ray examination

When first seen, the left breast presented a firm ovoid movable swelling 1 5 × 1 cm. After handling, it became definitely larger The x-ray film (fig 67A) showed a circular, sharply defined opacity in which faint striations were visible The child returned for observation three months later A needle biopsy was done. Smears showed many fat-containing cells, resembling the colostrum corpuscles of adults, and casts of dilated ducts in which the lumen was surrounded by many rows of hyperplastic secretory cells (fig 67B) The changes were of the type seen in the newborn, a similar hyperplasia is found at certain stages of secretory disease in adults Two years after the onset the breast had diminished in size and was soft. A year later scarcely any swelling could be felt.

Cysts of the breast at this age are extremely rare. Two cases of galactocele are recorded in the literature in boys aged fifteen months and seventeen months, respectively A consideration of Valentine's figures, Part I, explains how this could be brought about, and when one considers the stresses to which the infant breast is subject it is rather surprising that secretory cysts are not more prevalent in children.

Juvenile hypertrophy, apart from its association with tumors of the ovary, adrenal and pituitary, is seldom seen before the age of seven years *However, one case has been reported by Prouty* (1952) in a four-year-old boy following exposure to stilbestrol dust. The boy's ten-year-old sister was also affected The hyperplasia regressed when stilbestrol dust was eliminated from the environment. Hypertrophy without recognizable cause is fairly

LEFT

RIGHT

FIG 67. A

B

frequent in little girls, but is rare in boys before the onset of puberty The youngest recorded age in a boy was seven years (Ingleby, 1919)

Juvenile and adolescent hypertrophy differ radically from the infantile form. The mammary tissue consists of branching ducts similar to those of the normally developing female breast. There are no lobules and no lactiferous secretion The histology is the same in both sexes, but in boys there is a tendency for the gland to regress after puberty According to Geschickter (1943), less than 15 per cent of boys have any trace of enlargement at the age of twenty years In girls the enlarged gland usually develops into a normal female breast.

On the x-ray film the juvenile hypertrophied breast appears either as a rounded circumscribed area showing an irregular pattern corresponding to mammary parenchyma (fig 68) or as an irregularly outlined opacity from which long strands extend toward the chest wall. Figure 66 is a good example of this pattern, although, due to congenital malformation, dilatation of ducts is excessive. Slight dilatation of ducts may be expected in the developing breast.

Hypertrophy of the breast in young boys poses no problem Regression may occur spontaneously, but simple mastectomy, leaving the nipple in situ, has no undersirable aftereffect. It is quite otherwise in girls We hold that until the breast has reached its full development operative interference should be studiously avoided. The surgeon usually operates under the mistaken impression that the mass is a fibroadenoma or a cyst. Too late he may

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FIG 67 Hyperplasia of the left breast in a child aged twenty months. The breast was enlarged after birth. The swelling subsided at two months but returned at twelve months of age.

A. X ray films of left and right breasts The left shows a smooth rounded opacity with faint indications of trabeculation. Right breast is slightly hypertrophied although it did not appear so clinically

B Smear from needle biopsy shows casts of dilated ducts lined by many rows of secretory cells.



FIG 68 C 575 Precocious development of right breast Girl, nine years of age Increase in size of right breast noted two days. Left breast normal Sister aged twelve years has well-developed breasts Neither sister had menstruated X-ray film shows an irregular rather dense opacity, characteristic of the developing breast.

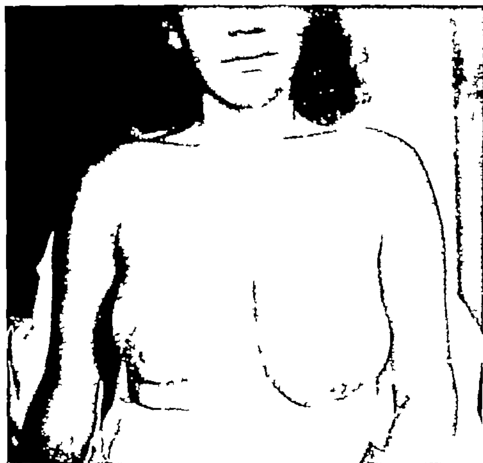


FIG 69 Hypertrophy of both breasts associated with recurrent multiple fibroadenomas.

Age eighteen years The left breast had always been larger than the right, even as a small child. Lumps were first noted in the breasts at about ten years of age. Menarche at eleven years, menses always regular twenty-eight to twenty nine days

When first seen both breasts were hypertrophied and extended below the thoracic cage. The left was larger than the right. A large fibroadenoma was felt beneath the left nipple. X ray therapy to breasts was given without benefit. A year later the fibroadenoma, which measured 7 × 5 5 cm. was removed.

Measurements of breast volume taken three and a half months after the operation were right breast, 670 cc. left breast 760 cc. At this time more masses were palpable in the left breast. The right breast presented a mass in the upper outer quadrant. A second operation for removal of fibroadenomas was performed on both breasts with good results

FIG 70. A





realize that he has blighted the girl's life by removing the only breast tissue the child has Fibroadenomas or cysts are very rare in little girls We have seen three cases of dilated lactiferous ducts opening onto the areola in children (fig 66), and one girl of eighteen years with hypertrophied breasts and multiple fibroadenomas gave a history of lumps in the breasts of the age of ten (fig 69) Masses of this type may be expected to disappear if the breast continues its normal development. In any case, surgical removal would be quite impossible without destroying the minute primitive ducts from which the adult mammary gland is derived Any harm which might result from noninterference would be less than this

Adult hypertrophy is most often an abnormal continuation of adolescent development, but sometimes has its origin in pregnancy or menstrual disorders The adolescent type is frequently familial. Abnormal enlargement is usually noted at a time when the breasts should have attained their full size. Essentially the condition is a continuation of the prepuberty pattern of growth after menstruation is established The ducts elongate and branch but lobules are scanty or absent. The epithelial structures are contained in long fibrous trabeculae separated by fat As time goes on there is irregular development of lobules, but large areas still present the adolescent pattern of ducts (figs 70–72)

Adult mammary hypertrophy of the second group is a form of dysplasia in which hyperplasia of glandular tissue is not balanced by involution. In one woman, aged forty-one years, enlargement of the breasts followed hysterectomy ten years before. The ovaries were intact. Each month, corresponding to the premenstrual phase, the breasts became swollen, but there was no cyclic regression. Sections showed considerable multiplication of lobules Many

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FIG 70 Hypertrophy of mammary gland—adolescent type. Female, age thirty years

A. & B Photomicrographs show ducts ending blindly in clubshaped swellings as in the adolescent and in the male hypertrophied breast.

C. Hypertrophied male breast age thirteen years is shown for comparison.

FIG. 71.

A



were irregular in their development The ductules were often dilated and some lobules were represented by a cluster of small cysts The ducts were elongated Some showed cystic dilatation. A few contained secretion. Fibrosis was also present but was not as extensive as in the first group (fig 73)

Gynecomastia, or hypertrophy of the male breast, is very common (figs 74–76) It is due to hormone imbalance with excessive circulation of estrogens Liver dysfunction, which interferes with the breakdown of estrogenic substances, is an important etiologic factor, as is administration of estrogens in older men with prostatic enlargement. In our series the most advanced hyperplasia was in a man of seventy-nine who had been taking stilbestrol for nine years for an enlarged prostate. Trauma was an exciting factor in some cases Many of the younger men were of nervous temperament amounting to neurosis in one case. E B Le Winn (1949) has drawn attention to mammary hypertrophy in cardiac patients, especially following digitalis medication

Forty-three males were examined by us Nine of them were normal or had epidermoid cysts In some of the nine the enlargement was due only to fat. The remainder were cases of gynecomastia. Carcinoma had supervened in three of these. The age

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FIG 71 A. & B C 1066 Familial mammary gland hypertrophy—adolescent type. Age thirty seven years Breasts started to develop at eleven years Menarche at thirteen years At fourteen years sought medical advice for large breasts Examination showed a very small woman with enormous breasts hanging down below the waist. They were somewhat nodular to palpation Pelvic examination negative. F.H. Mother has hypertrophied breasts Patient's two daughters aged six and ten years, respectively, show precocious breast development. Pathology Paraffin sections presented a few normal lobules, but in general the lobules were represented by groups of dilated ductules Slicer sections show

A. Fibrous trabeculae containing ducts and lobules separated by fat. Most of the structures were of the adolescent type. Many were halfway between adult and adolescent. The smaller ducts tended to be slightly dilated. Some contained secretion.

B Detail of abnormal 'lobules



FIG 72 C 277 Familial mammary gland hypertrophy—adolescent type. Age forty-three years The breasts had been enlarged since adolescence but growth had increased over the last fifteen years Married, no children although she wished for them. All the women of the patient's family had hypertrophied breasts. Slicer section shows a fibrous trabecula surrounded by fat. At one end of the trabecula there are some large lobules Elsewhere the lobules are poorly developed or replaced by ducts similar to those of the adolescent breast

incidence in our few cases paralleled that of the larger series recorded by Karsner (1946) and by Geschickter (1943). According to these authors, bilateral gynecomastia is comparatively rare. In our small series the x-ray film showed bilateral involvement in

FIG. 73. C 1518 Hypertrophy of mammary gland—adult type. Age forty-one years Following hysterectomy ten years previously both breasts became swollen before every period The swelling did not subside postmenstrually and the breasts gradually increased in size On examination enormous pendulous breasts were seen No masses were palpated Slicer sections A and B show a variegated form of dysplasia (mastopathy)



FIG 73 A



B

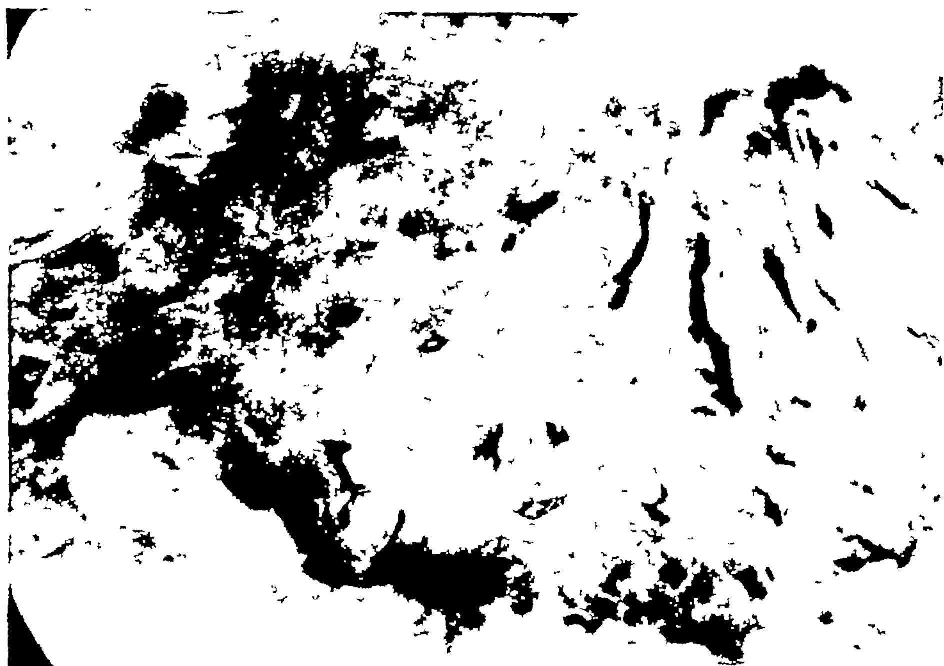


FIG 74. A



B

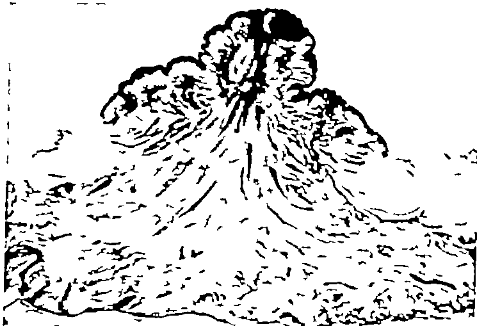


FIG. 75 C 313 Gynecomastia. Man age seventy-two years. Prostatectomy twelve years previously The breast shows a structure similar to that of hyperplastic fibrosis in the female.

twenty-two out of thirty-four cases The unilateral cases were mainly of traumatic origin.

Gynecomastia is apt to be confused clinically with fibroadenoma (a rather rare condition in our experience) or occasionally with

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FIG 74. C 214. Hypertrophied breasts—gynecomastia. First admission at the age of fourteen years for swelling of the left breast of four months duration. The breast had increased in size following trauma three weeks previously Clinical examination showed buttonlike swelling of left breast and slight swelling of right breast normal for adolescence. X ray film of the left breast showed a smooth rounded opacity corresponding to the mammary tissue

A. Slicer section from first operation shows branching ducts They resemble the early stage of development of the female breast, *Cf* fig 5

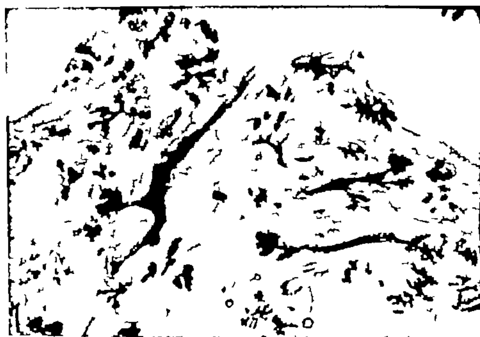
Patient returned two years later with a similar condition in the right breast The x ray film presented a rounded opacity like that previously seen in the left breast.

B. Slicer section shows a greater degree of development of ducts Some were considerably dilated.

FIG 76. A



B



C

FIG 76 C 1030 Gynecomastia. Extreme hyperplasia of both breasts Man, age seventy nine years. Self medication with stilbestrol for nine years.

A. X ray films of right and left breasts The mammary parenchyma resembles that of the adult female except that the breasts are smaller Irregular fluffy opacities are seen which in the female would be characteristic of adenosis

B. & C. Slicer sections from right and left breast show extreme proliferation of ducts. No lobules could be identified.

papilloma, carcinoma, or with inflamed sebaceous cyst or abscess The x-ray film will make the diagnosis clear

The appearance closely resembles that seen in juvenile hypertrophy In the pubertal type of hyperplasia the gland feels circumscribed and is shown as a well-defined opacity on the x-ray film. In older men strands of mammary parenchyma invade the surrounding fat. They must not be mistaken for the tentacles of carcinoma. Hypertrophied trabeculae course in the expected direction toward the nipple, whereas the tentacles of carcinoma

would be irregular. In carcinoma an irregular opacity corresponding to the tumor would also be visible.

Pathologically the enlarged breast is seen as a moderately firm grayish white mass, sometimes sharply circumscribed, sometimes with strands extending into the surrounding fat. It consists of branching ducts surrounded by a broad zone of intraductal tissue which is usually edematous and may contain scattered lymphocytes. The lining epithelium is hyperplastic. The ducts are slightly dilated and spurs of epithelial cells may project into the lumen. The over-all picture closely resembles that seen in the developing female breast (fig. 6). Although the possibility of lobular development cannot be excluded, we have been unable to find normally differentiated lobules in any of our specimens.

ADENOSIS

Adenosis may be defined as unencapsulated lobular hyperplasia Different forms have been described sporadically in the literature, notably by Dawson (1949). However, authors differ in their conception of what should be included in the syndrome they describe. Kiaer, for example, includes intraductal hyperplasia as well as adenosis under fibroadenomatosis Dawson does not distinguish between adenosis and intraductal hyperplasia Geschickter makes "adenosis" synonomous with Schimmelbusch's disease, but he gives a full account of lobular hyperplasia together with mazoplasia fibrosa under the heading of mastodynia. It is true that a minor degree of intraductal hyperplasia, confined to smaller ducts or ductules, is, so to speak, inevitable in adenosis. But this should not be confused with intraductal hyperplasia occurring as a major lesion mostly in larger ducts. Adenosis may be expected to be present as a minor component in cases of intraductal hyperplasia, and as in other dysplasias, borderline cases arise in which individual judgments differ. The point here is that intraductal hyperplasia is often a precancerous condition which threatens the life of the patient. It demands operation and must be distinguished from adenosis which in most forms is relatively

harmless Adenosis does not need immediate surgical intervention, provided carcinoma has been excluded by x ray examination.

Normally, mammary gland hyperplasia is seen in the newborn, at puberty, and during the menstrual and pregnancy cycles Imitations and exaggerations of these processes are found under conditions of hormone imbalance. Essentially, this is adenosis The boundary between physiologic changes and the pathologic entity called adenosis is therefore hard to define.

Irregular parenchymatous hyperplasia is an extremely common occurrence in the breasts of women. Studies of the mammary gland in monkeys, cows, goats, and laboratory animals generally, show that it is less frequent in lower animals, although in them it may be induced by various means X-ray studies demonstrate that the lesions, while they may preponderate in one breast, are nearly always bilateral. The adenomatous foci may be confined to one area or scattered generally over the breasts (figs 78, 82)

Adenosis matters not because of what it is, but because of what it may be. Until recently, although different forms were described in the literature, little had been done in the way of exact anatomical classification. The general impression was that these lesions were not precancerous, but recent studies show that a few may eventuate in carcinoma. The disorder accompanies other forms of dysplasia in the majority of patients under fifty years of age, but in many women who come to operation for breast tumor it is the only lesion found. More accurate diagnosis and a better evaluation of the importance of adenosis from the point of view of prognosis is therefore imperative.

As might be expected, parenchymatous hyperplasia occurs during the period of sexual activity In our series in which adenosis was the only lesion the youngest patient was sixteen (fig. 8) and the oldest was forty nine years The age distribution corresponded closely to that given by Geschickter under mastodynia (fig 77) As is usual in dysplasia, pelvic and thyroid disorders were common. Out of a hundred consecutive surgical cases where adenosis was the only lesion, twenty-one had undergone pelvic operations,

twenty-three had irregular menses without other pelvic manifestations, ten suffered from thyroid disorders. Some degree of sterility was frequent. Nine patients received hormone medication for a period of time before a mass appeared. "Nervousness" was very common. Allergies of one type or another were fairly frequent. Breast carcinoma occurred seven times in the next of kin, benign breast tumors eleven times, carcinomas of other organs twelve times. An interesting finding was the frequency of diabetes (37 per cent) in one or more members of the patient's family, although the patient herself was seldom affected.

As in other dysplasias the symptoms may or may not be distinctive. Premenstrual pain in young women is probably a mild manifestation of the disorder. In clinical cases a mass or multiple

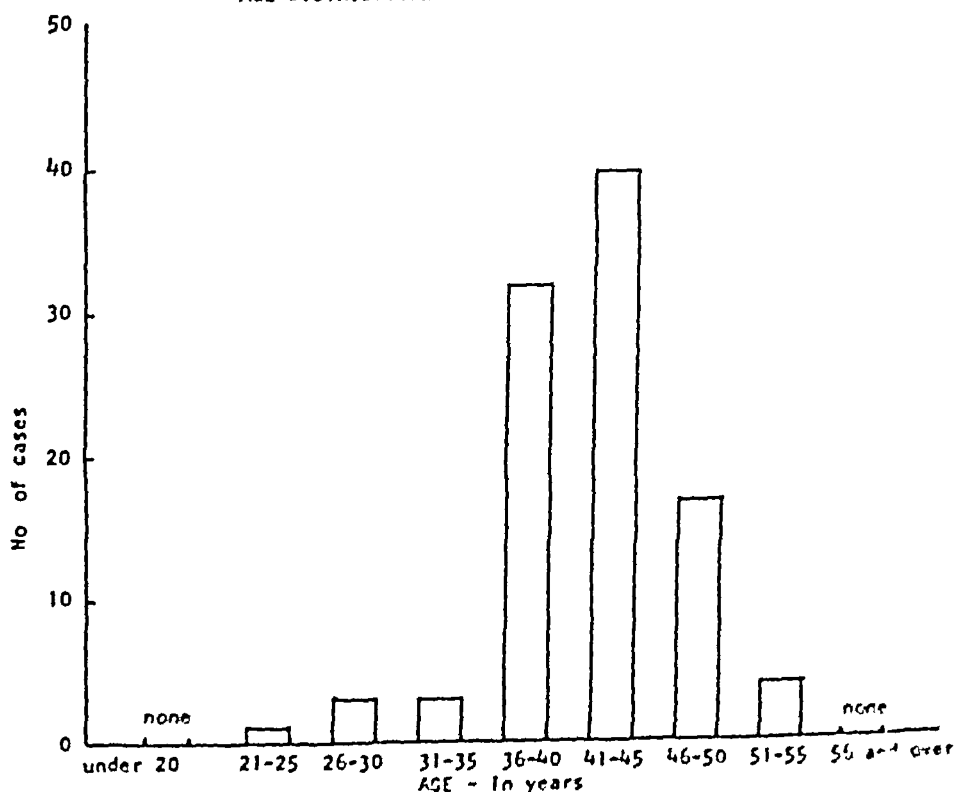


FIG 77

masses are felt. They are movable and are associated with pain, usually premenstrual, but occasionally midmenstrual In the more severe cases the pain becomes continuous, with exacerbations at these times A few women give no history of pain. The most characteristic feature of adenosis, and one which occurs in about half of all cases, is variation in the size of the masses The usual observation is swelling in the premenstrual phase with regression



Fig 78 C 407 Adenosis Age forty years Painless mass in left breast noted one week. The x ray film shows scattered poorly defined opacities throughout the breast. The right breast was similarly involved.

or even disappearance of the tumor postmenstrually. Occasionally there is swelling at the time of ovulation, with regression later. In several cases masses up to several centimeters in diameter, with redness of the overlying skin, have been noted, and a few days afterward, in the operating room, no tumor could be found. In some patients tumors have disappeared and reappeared over a period of time and have eventually become stationary. In one the regression lasted for many years It is not possible to state how many tumors vanish permanently, but many patients give a history of a lump which disappeared months or years before. These tumors were in all probability foci of adenosis.

On physical examination the tumors closely resemble cysts or fibroadenomas. The skin over them is sometimes reddened and the veins may be dilated When multiple masses are present the skin is often thin and tends to slide over the lumps. Although by no means diagnostic, this feature raises a suspicion that the diagnosis may be adenosis rather than cysts. In cases of this type where the tumors are stationary the question can be settled by x-ray examination.

Typical x-ray films show bilateral symmetrical lesions, more developed on one side than on the other. Areas of adenosis appear as fluffy or blurred opacities (figs. 78–81). They may be few or many. Their texture is reminiscent of ground glass. Breast trabeculae are visible in them. The margins are irregular for the most part, but occasionally an opacity is partly bounded by sharp curvilinear margins (figs 79, 80). These are sometimes formed by breast trabeculae, but apart from the trabeculae an incomplete capsule is occasionally found, as though the lesion had set out to be a fibroadenoma and had not yet finished the job (fig 79); and this is precisely what is seen in many pathologic specimens (figs. 93, 112) In women with fatty breasts the opacities are isolated between clear zones of fat. In generalized adenosis the films are dotted over with fluffy opacities which may be confluent (fig. 81) The differential x-ray diagnosis will be discussed in connection with other dysplasias.





FIG 80. C 433. Adenosis simulating cysts Age thirty-two years Mass in left breast two months, first noted before a period It increased in size before the last period On examination a nodular mass extended

At first sight the fresh pathologic specimen may show nothing to distinguish adenosis from normal breast tissue However, when exposed to the air, a few pink spots and an occasional small pinkish patch may be revealed. In some specimens the patches are larger and more obvious In sclerosing adenosis they are often yellowish. On palpation the breast is more or less nodular The nodules give the impression of firm masses, but when cut into they seem to melt with the surrounding breast. The only firm areas are those in which a fibroadenoma is beginning to form. Under the dissecting microscope it is sometimes just as difficult to draw the line between the earliest phase of adenosis and normal lobules Clinically it is easy to mistake an outlying group of lobules for a tumor and the surgeon may remove them. Apart from such doubtful lesions adenosis may, in theory at any rate, be classified into four types of lobular dysplasia. A fifth type, i.e , "secretory adenosis," could be included, but this differs in many respects from the others and is moreover an essential part of the entity we have named secretory disease. It will therefore not be considered here.

The purpose of classification is to predict the outcome of the lesions A hard and fast barrier does not exist between types More than one type is often present, but usually one is predominant and evaluation is made accordingly Under the dissecting microscope the extent of the foci of adenosis and the types of lobules (with the exception of type C) of which they consist are readily recognized

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through most of the left breast. A similar smaller mass could be felt in the right breast. The clinical diagnosis was multiple cysts and certainly by palpation no other conclusion could have been reached. But repeated roentgenograms failed to reveal cysts There were instead multiple irregular opacities of the "ground glass" type, separated by clear zones of fat. At operation two pieces of firm breast tissue were removed. They contained neither cysts nor tumor Microscopically, there were areas of adenosis type B separated by dense connective tissue in which remains of involuted lobules could be made out



FIG. 81. C 644. Generalized adenosis Aged thirty-five years. Movable mass 1 cm. in diameter noted accidentally in upper part of breast one month ago No pain. X-ray film shows areas of increased density which are practically confluent. They extend from the base toward the nipple A denser area is seen in the upper portion just above the marker. A large vessel (arrow) enters the area—a sign of active proliferation. *Cf.* fig. 43, early pregnancy. The paraffin section showed adenosis with transition to mazoplasia cystica.



FIG 82. C 620 Generalized adenosis—slicer section. Age thirty-seven years. Slicer section of breast through nipple area. Large numbers of lobules, irregular in size and degree of development, are seen at the periphery of the gland. The hyperplasia is most in evidence toward the upper outer quadrant near the site of a small carcinoma (not included in the section) Paraffin sections showed adenosis type C.

Type A (fig 83) is characterised by lobular hyperplasia with normal development of ductules Under the dissecting microscope, the lobules have a dense bushy appearance. Many large lobules are seen or, alternatively, smaller ones lying close together In early adenosis the affected lobules present a complete layer of basal cells in most of the ductules The ductules are lined by many more cells than usual. In places they push up the epithelium and sometimes even occlude the lumen of the duct. Some of these cells show blunt processes, the first sign of transition to myoid. As the cycle advances, there may be a continuous sheet of myoepithelial cells lying on the basement membrane. Their processes are occasionally seen merging with it. Practically all specimens show

single myoid cells lying outside the basement membrane. These possess two or more fibrillary processes which often surround the duct and at times replace the membrane. The nuclei are generally small and have pointed ends. In the prelobular ducts the hyperplasia is even more intense, and in trichrome preparations the sheaves of red-staining cells are very easy to see. It is logical that the myoepithelium should be exceptionally well developed in these ducts since expulsion of the milk from the lobules depends to a great extent on myoepithelial contraction in their walls At the time of the menstrual period it is common to find only a few ducts undergoing involution, but in some cases the entire lobule degenerates (fig. 90C) It is then replaced by fibrous tissue With suitable technic it is possible, in favorable specimens, to trace the outlines of the involuted hyperplastic lobules

Type B (figs. 85, 86) presents lobules which consist of a few more or less dilated ductules The lobules are numerous, but owing to failure to form dichotomous branches, their development is incomplete. Cystic dilatation takes place whenever the walls of a duct or ductule proliferate as a whole instead of at specific growing points The channels will then become wider and longer. The amount of dilatation depends on the degree of development of the lobules before the abnormal stimulus reaches them and on the intensity of the stimulus

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FIG 83. C 331. Adenosis, type A. Age forty-four years. Indefinite mass in right breast noted seven days. Hysterectomy three years before. Ovaries not removed. The x-ray film showed an opacity resembling fibroadenoma but the edges were not smooth At operation no tumor was found. Microscopically there were large hyperplastic lobules Myoepithelial cells were especially conspicuous. Nearby were some small apocrine cysts with conspicuous myoepithelial cells (fig 103), probably a part of the same process.

A. Slicer section shows moderately large lobules lying close together. Magnification approximately ×5.

B Paraffin section: part of a lobule. The epithelium is hyperplastic Striae from the myoepithelial cells are seen as fine blurred lines emerging from the ductule in the right half of the picture and lying over the adjacent ductules ×80

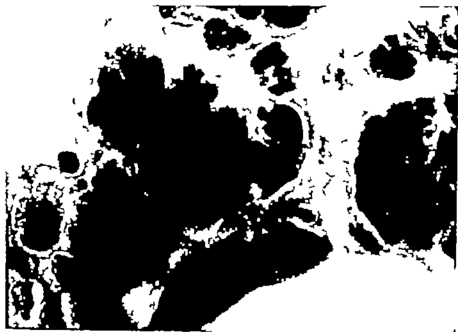


Fig 83 A

B

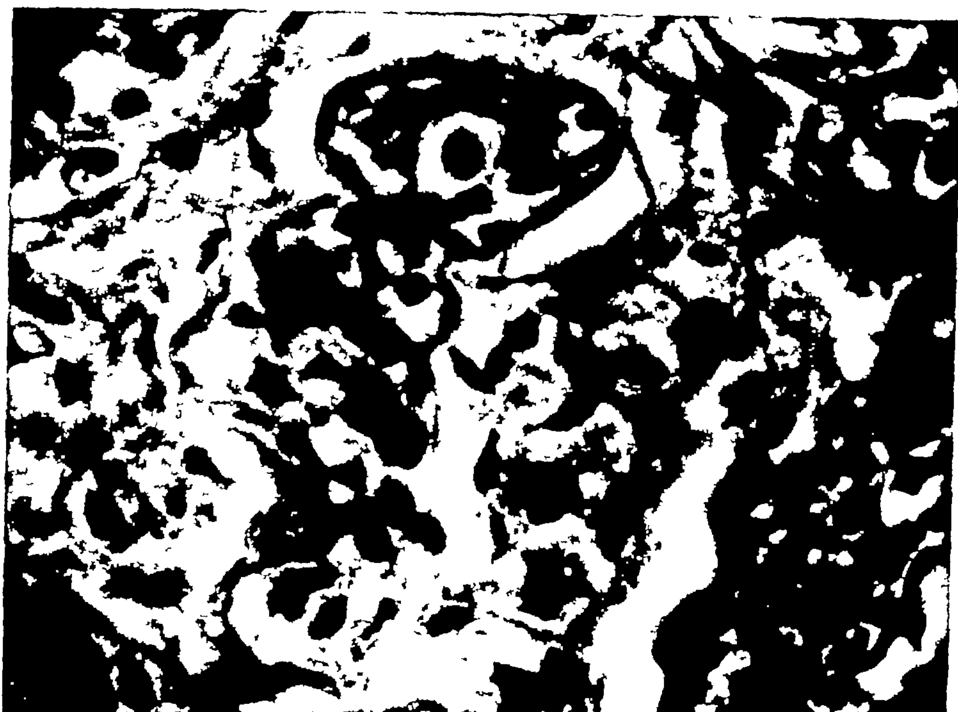


FIG. 84 C 772. Postmenstrual involution of ductules from a case of adenosis Age twenty-three years. A ductule near the center of the field shows in the upper part, cut transversely, vacuolization of the basal cells and degeneration of the superficial epithelial layer. The longitudinal portion of the ductule in the center of the field as well as another ductule near the edge is filled with degenerating cells. Between them the remains of a ductule can be made out. The only recognizable elements are the branching myoepithelial cells.

Under the dissecting microscope the affected lobules are seen as groups of small cysts. Their general conformation is similar to the club-shaped ducts of the adolescent and also to formations due to lack of lobular development seen in the mazoplasia of Cheatle and Cutler No confusion arises in practice because in the adolescent the same conformation is present evenly in all of the terminal ducts, whereas in mazoplasia the lobules, if they can be called lobules, are extremely sparse In adenosis, low-power magnification shows a large group of lobules lying close together. Occasional lobules of this type are common in all breasts. When

they occur singly or in small numbers they can scarcely be considered pathologic. The diagnosis of adenosis B depends on the numbers of lobules and the size of the area involved. Histologically, adenosis B shows groups of lobules with sparse, dilated ductules or groups of small cysts Albuminous secretion is often present in the lumen. Rarely, tiny droplets of fat are seen. The secretion is similar to that seen in the premenstruum but more abundant It would seem to stagnate in the more dilated ducts The epithelial cells may or may not be hyperplastic, depending probably on the age of the lesion. In the more dilated ducts they may be flattened. A few fields may show intraductal proliferation with obliteration of the lumen. The myoepithelial cells are usually numerous and conspicuous The intralobular tissue is extremely edematous in many lobules, but may be densely fibrous in others In the edemat-

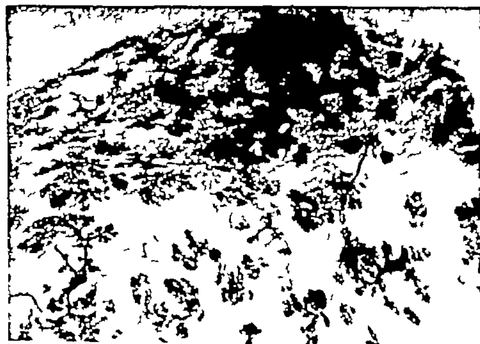


FIG 85 C 231 Adenosis, type B Age fifty-one years Slicer section from a case of adenosis type B The lobules are numerous but their development is irregular and they consist of fewer ductules than normal. Under higher power the ductules were seen to be dilated.



FIG 86. C 882 Adenosis, type B. Age thirty-five years. Paraffin section from a case of adenosis type B. Part of a lobule showing dilated ductules and marked myoepithelial hyperplasia

ous lobules mononuclear cells are rather numerous. The state of the myoid must be carefully noted If there is no hyperplasia, suspicion that the diagnosis may be type C rather than B should be aroused In adenosis B, involution is possible but less likely than in type A. The area may be replaced by fibrous tissue. If not, the condition is likely to progress to mazoplasia with cysts. There is also a strong tendency to the formation of fibroadenomas.

Type C (fig 87) is difficult of diagnosis because it closely resembles type B and is only distinguished from it by study of the myoepithelial cells Adenosis C is nearly always present in the vicinity of the tumor in young women with carcinoma and must therefore be regarded with grave suspicion In these breasts lobular hyperplasia may be widespread, but there are no large cysts. The lobules consist of dilated ductules as in type B The

epithelium, especially of the basal cells, may show proliferation, but myoepithelial cells are inconspicuous or absent. The essential factor seems to be a disturbance in the organization of the walls of the ductules Under these circumstances, undifferentiated cells may accumulate within a duct In some cases the cells may degenerate. If they do not degenerate and proliferation persists, the condition passes over into the type of epitheliosis which is a direct precursor of carcinoma. The problem of precancerous conditions and their relation to myoepithelial cells will be taken



Fig 87 C 16 Adenosis type C. Age twenty-eight years Indefinite swelling left upper outer quadrant noted ten days. Patient is a monovular twin. Her sister had a radical mastectomy four months previously for a carcinoma in the left upper outer quadrant and has since died. Mother died of breast carcinoma at sixty-eight years. Father died of carcinoma of the intestine. On account of the family history the tissue from the upper outer quadrant was removed. Patient has remained well for five years. Paraffin section shows hyperplasia of basal cells, but scarcely any recent differentiation of myoepithelial cells.

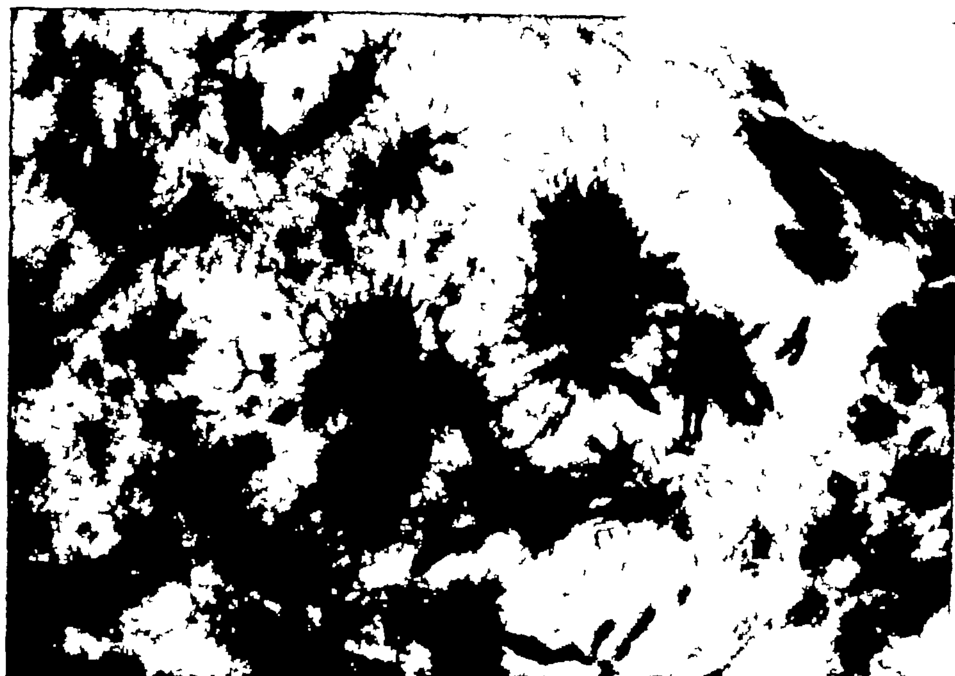


FIG 88 C 426 Adenosis type D (sclerosing adenosis). Age forty-four years Slicer section shows several masses bordered by tangled fibrils. The centers are mostly too dense for the structure to be made out, but ductules are discerned in some places.

up more fully in a subsequent chapter. Adenosis type C is stressed because of its possible prognostic import. In many cases absence of myoid occurs only in certain areas We do not know why this is so, but unless this is accompanied by hyperplasia of myoepithelium elsewhere in the section, a reserved prognosis should be given.

Type D (figs. 88, 89) is the sclerosing adenosis of Urban and Adair (1949). The areas of adenosis vary from a centimeter or more in diameter to minute specks scarcely visible to the naked eye. They may be yellowish in color. When of recent origin they are soft. Later they are firm and fibrous. The myoepithelial origin of these masses was noted by Masson in his textbook (1923), but seems to have been subsequently forgotten, at least by English pathologists. In the early stages the microscopic section shows a mixture of epi- and myoethelial cells, the myothelium pre-

ponderating The nuclei are large and vesicular, the myothelial cells show thick striated processes (fig 89) In some areas the picture resembles that seen in the earliest stages of pregnancy Later the nuclei are smaller, the myothelial cells develop long fibrous processes Eventually they take collagen instead of muscle stain. Some cells undergo hydropic degeneration. The epithelial cells are few and degenerated as in the normal menstrual phase. The final stage is a fibrous scar Under the dissecting microscope the patches are seen as tangled structures often containing very fine fibrils They are recognizable, but of course their minute components cannot be made out.

Adenosis D follows the rule that where myoepithelium is well developed the lesion is never precancerous It does, however, mimic carcinoma very closely In paraffin sections rows of myoid

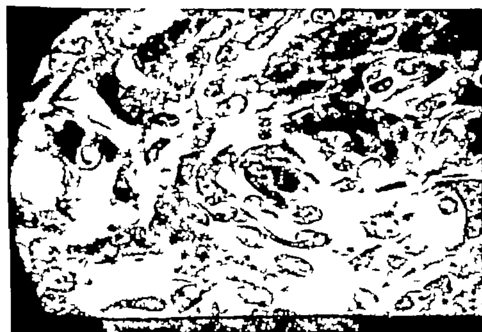


FIG 89 C 93 Adenosis type D — early stage. Age forty-one years. Paraffin section shows a very early differentiation of myo- and epithelial cells, resembling that seen in pregnancy [*cf* fig 35] × 1000



A

FIG. 90. C 1173. Adenosis — recurrent tumors Age twenty-nine years. The patient was first operated on in 1950 for a mass in the left breast which showed only hyperplastic lobules. In 1952 she complained of a painful mass in the left upper outer quadrant of seven months duration It appeared at the time of the menses and later subsided On examination five days after a period the upper outer quadrant of the breast was found to be swollen Two days later the swelling had disappeared and all that could be felt was an indefinite thickening with one narrow cordlike duct. The operation specimen presented firm, slightly nodular breast tissue speckled with minute ducts. Slicer sections and paraffin sections showed adenosis, chiefly type B, with lobular involution

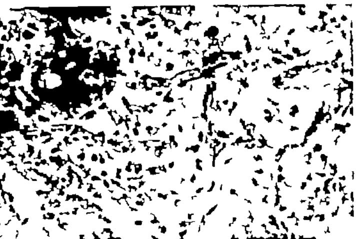
Two years later the patient returned with a precisely similar condition in the upper outer quadrant of the right breast, except that the swelling occurred somewhat later in the cycle When seen immediately before the onset of a period only a nontender granular thickened area was felt. Both operations were performed when the swelling had nearly subsided, but the second specimen showed a more active stage of regression

A The x-ray shows an indistinct opacity with a "washed out" appearance in the right upper outer quadrant The quality of the opacity is similar to that seen in involution following lactation.

B Slicer section shows an area of lobular involution. Most lobules are represented by a few stumpy ducts. The intervening tissue is edematous.

C. Recently degenerated lobule An intralobular duct is visible on the left To one side are clusters of nuclei, the remains of hyperplastic ductules Elsewhere the lobular tissue is replaced by an area of





B Fig 90 C







A

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C Recently degenerated lobule. An intralobular duct is visible on the left. To one side are clusters of nuclei, the remains of hyperplastic ductules Elsewhere the lobular tissue is replaced by an area of



C

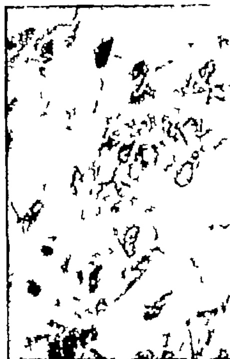


FIG 90



B



nuclei surrounded by fibrils may be mistaken for epithelial invasion. Careful histologic technic coupled with experience is required if error is to be avoided.

Premenstrual or intermenstrual swelling of the tumors in adenosis is due, as in the normal breast, to parenchymatous growth, imbibition of fluid, and vascular dilatation. The changes are exaggerated in adenosis. In type A the lobules are obviously increased in size, in type B the dilated ductules lie farther apart and take up more space. Disappearance of lobules in the postmenstrual phase together with absorption of fluid accounts for shrinkage of the tumors (figs. 84, 90).

Classification of types of adenosis is only of value in so far as it allows prediction of the ultimate outcome. To achieve this, extensive follow-up of patients is required. Fortunately, in the x-ray film we have a tool whereby the progress of a case may be watched, provided certain pitfalls are avoided. Changes in breast volume are hard to detect by x-ray because of the difficulty of preventing alterations in the shape of the organ. The flabby postmenstrual breast may appear larger on the film simply because it undergoes flattening, although in fact its volume is smaller. The same error could prevent accurate appraisal of the masses, but since the masses are firmer, artefacts probably do not occur to the same extent. Changes in the area of adenosis have been detected in a few patients who have been x-rayed at intervals, and since these coincided with the clinical impression and measurements they probably represented a real difference. The objections stated above could be valid when single areas of adenosis are under scrutiny. They do not hold for fresh lesions Newly formed masses

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FIG. 90 (continued).

of edema in which engorged capillaries, remains of nuclei and cell debris are seen. This goes far beyond what is seen in normal cyclic involution Paraffin section × 480

D. and E. Two stages of involution of ductules. Oil immersion, × 1000. In D remains of epithelial cells are still seen. In E only degenerated myoepithelial cells remain.

as well as disappearance of previously noted tumors can be diagnosed with certainty

In certain patients, it has been possible to trace the development of the lesions over varying periods Some adenomatous masses disappear by a process similar to normal postmenstrual involution (fig 90) Some disappear after pregnancy, some, especially in longstanding cases, are replaced by fibrous tissue (fig 92) Some develop into mazoplasia cystica (fig 98) Some form fibroadenomas (figs 79, 93, 112) All these changes have been observed. Collateral evidence of resolution of the lesions is afforded by the long histories of patients with painful breasts and lumps that come and go and eventually subside at the time of the menopause. These are almost certainly cases of adenosis Most of the patients have no further trouble. The x-ray film often reveals fibrous patches, bilateral and more or less symmetrical in distribution, in elderly women. The most likely interpretation of these appearances would seem to be fibrosis following adenosis The lesions might be thought of as quiescent. Unfortunately, the facts do not warrant this assumption. In women x-rayed for carcinoma, a malignant lesion may be seen in one breast, and in the corresponding position of the contralateral breast, an opacity resembling adenosis or fibrosis (fig. 201) It is often not possible to determine the original form of adenosis Type C may be suspected, but proof is lacking The problem will be fully discussed under carcinoma.

Another common form of fibrosis which follows involution of adenosis is hyperplastic fibrosis Opacities appear on the x-ray film which are smaller and more uniform than those of adenosis The change is likely to be observed first in the central or upper portions of the breast. It is very common at or after the menopause and we have been able to trace the transition from adenosis to fibrosis on x-ray films and in pathologic sections While this type of fibrosis is not necessarily precancerous, it is intimately associated with certain forms of carcinoma Hyperplastic fibrosis and its possible relation to carcinoma will be discussed in detail in Part III



A

FIG 91 Adenosis Recurrent tumor The patient, a multipara aged thirty-one years, noted a somewhat tender lump above the left areola one week before the onset of the menses. The periods were irregular At that time the mass, 3 cm in diameter, resembled a cyst on palpation. After the period it could no longer be felt.

A. The x-ray film shows an area of "ground glass" opacity in the upper part of the breast (arrow). The texture of the opacity is not uniform

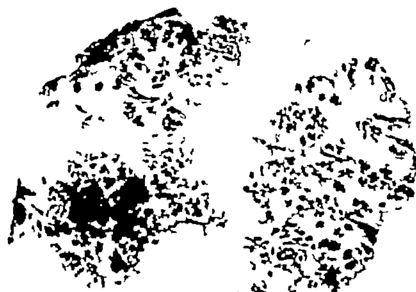


FIG. 91 B

as would be characteristic of cyst or fibroadenoma nor does it resemble them in shape. The sharp margins are made by fibrous trabeculae which enclose the area. A few small fluffy opacities are seen elsewhere in the breast. At operation adenosis was the only lesion found.

B Slicer sections from operation specimen.

Foci of adenosis are most often bilateral and multiple. Because of the accompanying pain the patient's attention is focused on the mammary glands She is more often than not a nervous type of person and the fear of cancer is constantly before her The fact that she is emotionally disturbed goes a long way toward making the condition worse. Should one take the gloomy view that adenosis is a precancerous lesion the only remedy would be to remove both breasts, a procedure that even the most radical surgeon would hesitate to recommend Warren (1940) found that carcinoma was four times as common in women with dysplasia as in women with normal breasts, but his figures cannot be applied to adenosis without some qualification. Adenosis B, which comprises some three



A

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twins whose mother had died of carcinoma One sister, aged twenty-eight years, developed carcinoma in the upper outer quadrant of the left breast and died with multiple metastases twenty-one months later Four months after her sister's operation the other twin reported a swelling at a site corresponding to her sister's tumor No definite mass was present, but in view of the family history the area was excised No pathologic condition could be detected grossly, but microscopically the breast lobules were numerous and consisted of groups of dilated ductules In most of them, myoepithelial cells were scanty or absent (fig 87) Comparison of slicer sections revealed that the sisters had a similar type of mammary parenchyma Periodic examinations of the surviving sister by her family doctor over the last five years have not disclosed any further trouble. Since 80 per cent of identical twins are liable to identical tumors, the operation may well have prevented the development of carcinoma In cases of carcinoma, myoepithelial



FIG 93 C 716 Age thirty years Slicer section Early formation of fibroadenoma in a focus of lobular hyperplasia.

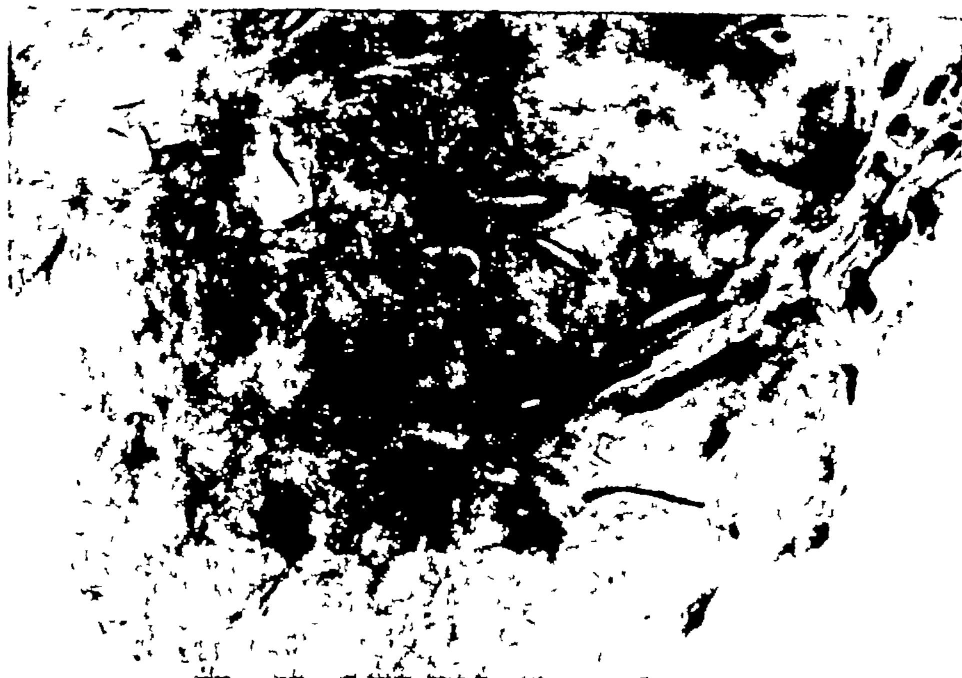


FIG 92. C 552. Fibrosis following adenosis Age thirty-eight years Tender mass in the upper outer quadrant of the left breast gradually increasing in size for ten months. On examination several cystlike masses were felt in both breasts. The mass in the upper outer quadrant was removed at operation It consisted of fibrous tissue with occasional aggregations of lobules There was no tumor

Slicer section: The fibrous pattern is not that of mazoplasia fibrosa, but is characteristic of lobular involution A very early stage of hyperplastic fibrosis can be discerned in the section

fourths of the cases, is definitely not a precancerous lesion and the same may be said of type D. Type A is probably the first stage of proliferation It is often found with other types and could progress to B or D. Hyperplastic lobules may resolve completely or be replaced by fibrous tissue. Failing this, a small focus of adenosis may develop into a fibroadenoma.

The one form of adenosis which may be dangerous is type C It is deceptively like type B on superficial examination and can only be recognized by the scarcity or lack of myoepithelial cells Our attention was first directed to this type by a case of monovular

twins whose mother had died of carcinoma. One sister, aged twenty-eight years, developed carcinoma in the upper outer quadrant of the left breast and died with multiple metastases twenty-one months later Four months after her sister's operation the other twin reported a swelling at a site corresponding to her sister's tumor No definite mass was present, but in view of the family history the area was excised. No pathologic condition could be detected grossly, but microscopically the breast lobules were numerous and consisted of groups of dilated ductules In most of them, myoepithelial cells were scanty or absent (fig. 87) Comparison of slicer sections revealed that the sisters had a similar type of mammary parenchyma. Periodic examinations of the surviving sister by her family doctor over the last five years have not disclosed any further trouble. Since 80 per cent of identical twins are liable to identical tumors, the operation may well have prevented the development of carcinoma. In cases of carcinoma, myoepithelial



FIG 93 C 716 Age thirty years. Slicer section Early formation of fibroadenoma in a focus of lobular hyperplasia.

cells are rarely present in the tumor areas. In microscopic sections where the diagnosis of malignancy is in doubt, the presence of well-developed or hyperplastic myoepithelial cells *in the tumor* indicates a benign lesion, their absence is strongly suggestive of carcinoma

Foulds's studies (1956) on progression in mammary tumors of mice indicate that more care should be taken in the follow-up of disappearing and recurrent foci of adenosis than is usually accorded these patients The recurrent plaques which were the basis of carcinoma in his mice may be homologues of foci of adenosis in women (fig. 194). Hitherto we have thought of recurrent tumors as benign, but we have now observed at least four cases in which an apparently recurrent tumor evolved eventually in clinical carcinoma. Cases of this kind are exceptional and the surgical removal of a nonexistent tumor hardly seems an appropriate form of treatment. The same may be said of tumors that come and go. At this stage the masses are benign and generally remain so. But the fact that carcinoma is a possibility, albeit a remote one, does emphasize the need for a certain caution in dealing with adenosis. Although as a rule no treatment is necessary, patients with adenosis should be kept under observation. Biopsy of a "lump" is useless, because the surgeon has no way of knowing which among many masses to excise. By far the best method is periodic x-ray examination. Granted good technic, an experienced radiologist will be able to pick out a small carcinoma or even at times a precancerous lesion from the multiple masses present in a woman's breast (figs. 183, 193)

In summary it may be said that disappearing tumors in young women may be safely let alone, but return of the tumor with the acquisition of a permanent status makes x-ray examination mandatory. Roentgenologic check-ups would be a useful precaution in any case and recovery may be helped by the reassurance they give If on a technically satisfactory film no tumors but only ill-defined opacities are visible, the clinical diagnosis of cyst or fibroadenoma should be reconsidered.

The question in what proportion of cases does adenosis precede

carcinoma can only find its answer in years of study and follow-up of patients An exact estimate of numbers of women with adenosis is impossible to obtain at this time. It is quite likely that most women have hitherto considered premenstrual breast pain part of the ills that women must put up with and do not consult a physician. Now that mammary gland ailments have been publicized and cancerophobia has been instilled into the population many more women seek advice. The condition is habitually labeled "cystic disease. The case is sent to a surgeon who operates, but finds nothing Meanwhile, in a few, a very few patients, a nodule indistinguishable from all the other lumps in the breast may be the site of development of a carcinoma (figs 186, 195) These are the cases in which expert radiology can do the most good. The tient with adenosis need not undergo surgery Periodic x-ray examination will enable a carcinoma to be dealt with before it becomes a threat to life (fig 199) Although the clinical aspect must always be taken into consideration, the opinion of the experienced radiologist as an ancillary means of diagnosis may well acquire the same standing as that of the pathologist.

MAZOPLASIA FIBROSA

The term "mazoplasia" was originally coined by Cheatle to denote diffuse nodular painful breasts He believed that it was an entity sui generis" and that it was never accompanied by cyst formation. However, his description and illustrations show that adenosis, especially type B, is included in his syndrome Mazoplasia was also described by Semb (1928) under the name of fibroadenomatosis simplex (microcystica), or if cysts were present, fibroadenomatosis cystica. Contrary to Cheatle s view, Semb thought that fibroadenomatosis cystica—mazoplasia cystica in our terminology, was a sequel of fibroadenomatosis simplex, or Cheatle s mazoplasia. The truth seems to lie between the two extremes

In order to stress certain features common to both, we originally designated mazoplasia fibrosa and mazoplasia cystica as mazoplasia

group I and mazoplasia group II, respectively. This terminology proved unnecessarily complicated and had not the advantage of being self-explanatory. It has therefore been discarded. Cheatle's work of the 1920's marks an epoch which should not be lightly forgotten. Our interpretations have changed with the lapse of time, but Cheatle's observations, descriptions, and illustrations may still be studied with profit. We therefore retain "mazoplasia," although with some qualifications of its meaning, as a fitting tribute to a great man.

In our early roentgenographic studies of the mammary gland we were struck by a group of cases in which the breast was uniformly dense and homogeneous. On the x-ray film it resembled the normal gland of adolescence. Comparison with pathologic sections showed that we were dealing with mazoplasia of the type described by Cheatle—mazoplasia fibrosa of our classification. Mazoplasia fibrosa is most often seen in women around the age of thirty years. As in all dysplasias the lesions may be general or focal and are practically always bilateral. The patient complains of tender lumpy breasts. The pain is usually premenstrual and seldom severe. Diffuse or circumscribed nodular, sometimes flattened, areas are felt on examination, the upper quadrants being commonly affected. The condition may remain more or less stationary for years and disappear at the menopause. A change in hormone balance, such as occurs in pregnancy, may restore the breast to normal. On the other hand the possibility of progression to mazoplasia cystica and mastopathy cannot be ruled out Fibroadenomas, single or multiple, are very common We used to believe with Cheatle that mazoplasia of this type was never precancerous However, recent experience suggests that there are exceptions even to this rule (fig 177).

The nodules of mazoplasia fibrosa have to be distinguished from areas of adenosis and from cysts. The diagnosis is often difficult clinically, but can be made with comparative ease on the x-ray film. The x-ray film of the breast in mazoplasia fibrosa closely resembles that of the adolescent or immature breast and

may be indistinguishable from it (fig. 94) Both are small and show the same uniform density, but in mazoplasia the subcutaneous margin of the gland may be bosselated. When the lesion is localized in one quadrant the smooth "ground glass" opacity is confined to that area. The coexistence of fibroadenomas might be expected to confirm the diagnosis, but since these tumors are common in adenosis and in mazoplasia cystica, this sign cannot be relied upon.

Pathologically the gross appearance of the breast is fairly characteristic. The gland is small and tough. It often feels nodular, but when the nodules are cut down upon there is no obvious lesion. The cut surface looks normal. In both slicer and paraffin sections the outstanding feature is hyperplasia of the fibrillary (intraductal) zone which lies immediately beneath the epithelium of the ducts (figs 94–96) The duct presents a collar of fibrillary tissue many times the diameter of its lumen This may cause compression atrophy of the epithelium with narrowing or complete obliteration of the lumen (fig 96) In other ducts the epithelium proliferates to some extent and these ducts will show mild dilatation. There is considerable diminution in the number of lobules In their place one finds groups of club-shaped ducts Their general conformation simulates the pattern of terminal ducts in the adolescent breast. However, there are important differences In mazoplasia the breast shows sparse ducts and disproportionate thickening of the intraductal tissue. During development the ducts are crowded together and proper proportions between the different components of the duct wall are maintained. Under the dissecting microscope the contrast between the closely packed ducts of the adolescent and the sparse thickened ducts of mazoplasia is obvious No less obvious is the distinction between the pseudolobules of mazoplasia and normal breast lobules in which the ductules are so close together, especially in the last half of the cycle, that they are difficult or even impossible to make out under the low magnification used.

Focal fibrillary hyperplasia of the intraductal tissue when long

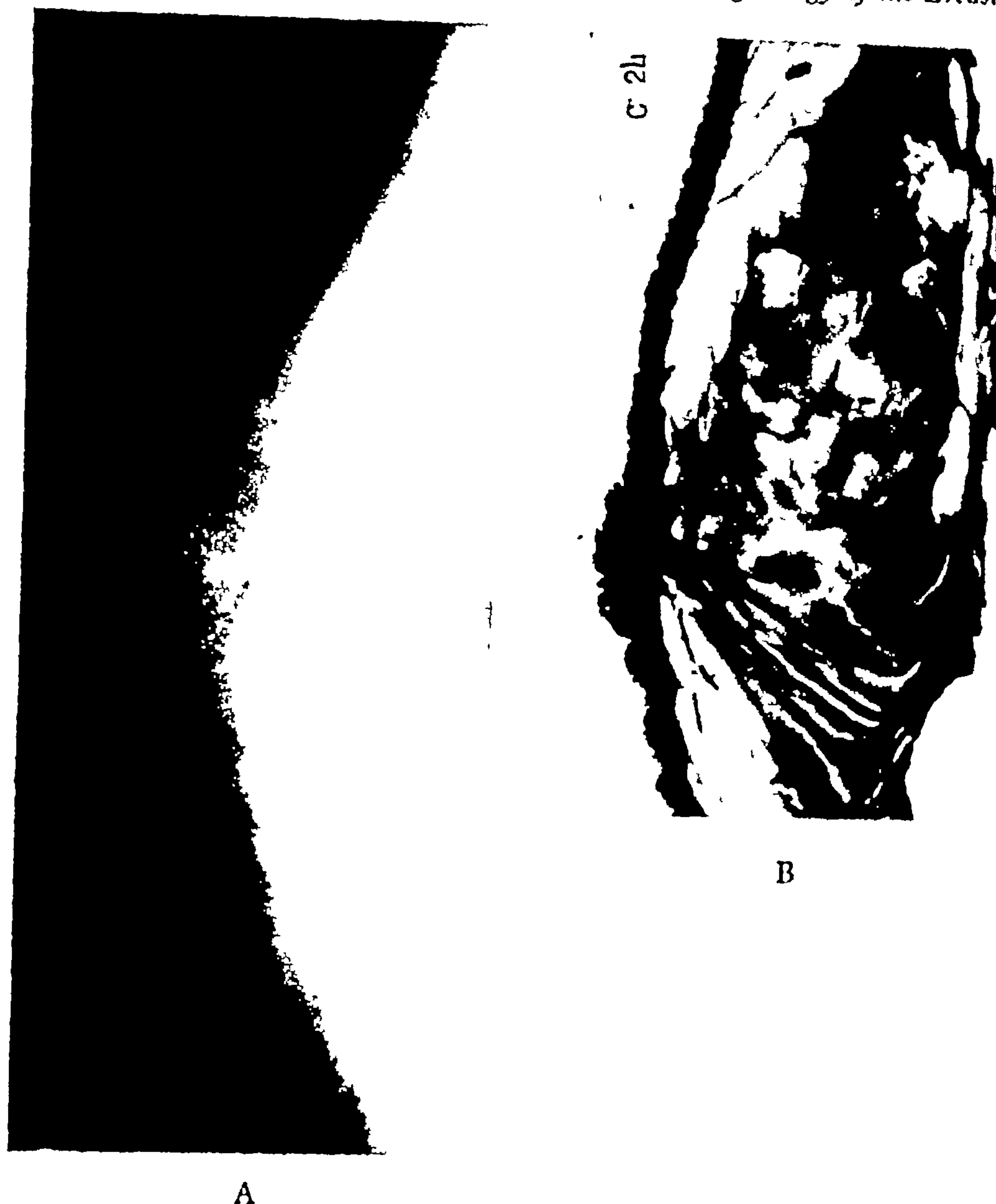


FIG. 94. C 24 *Mazoplasia fibrosa* Age thirty-four years

A. X-ray film: the mammary parenchyma is dense, except for a few fatty areas

B. Slicer section shows very marked thickening of the intraductal layer A fibroadenoma is seen at the base of the breast The upper portion of the breast shows a number of proliferated ducts with formation of poorly developed lobules A minute fibroadenoma is seen among them

continued leads to fibroadenoma of the intracanalicular type which often accompanies mazoplasia (fig 111) Microscopic fibro-adenomas are commonly present in these breasts Most of them seem to disappear when the normal physiologic balance is restored.

The above description applies to the pure form of mazoplasia



Fig 95 Mazoplasia fibrosa. Age thirty three years. Simple mastectomy for mastodynia. Last menstrual period twenty four days before. Slicer section through entire breast. The lobules are represented only by collections of dilated terminal ducts and even these are scanty Toward the center broad collars of fibrous tissue surround the remains of duct epithelium.

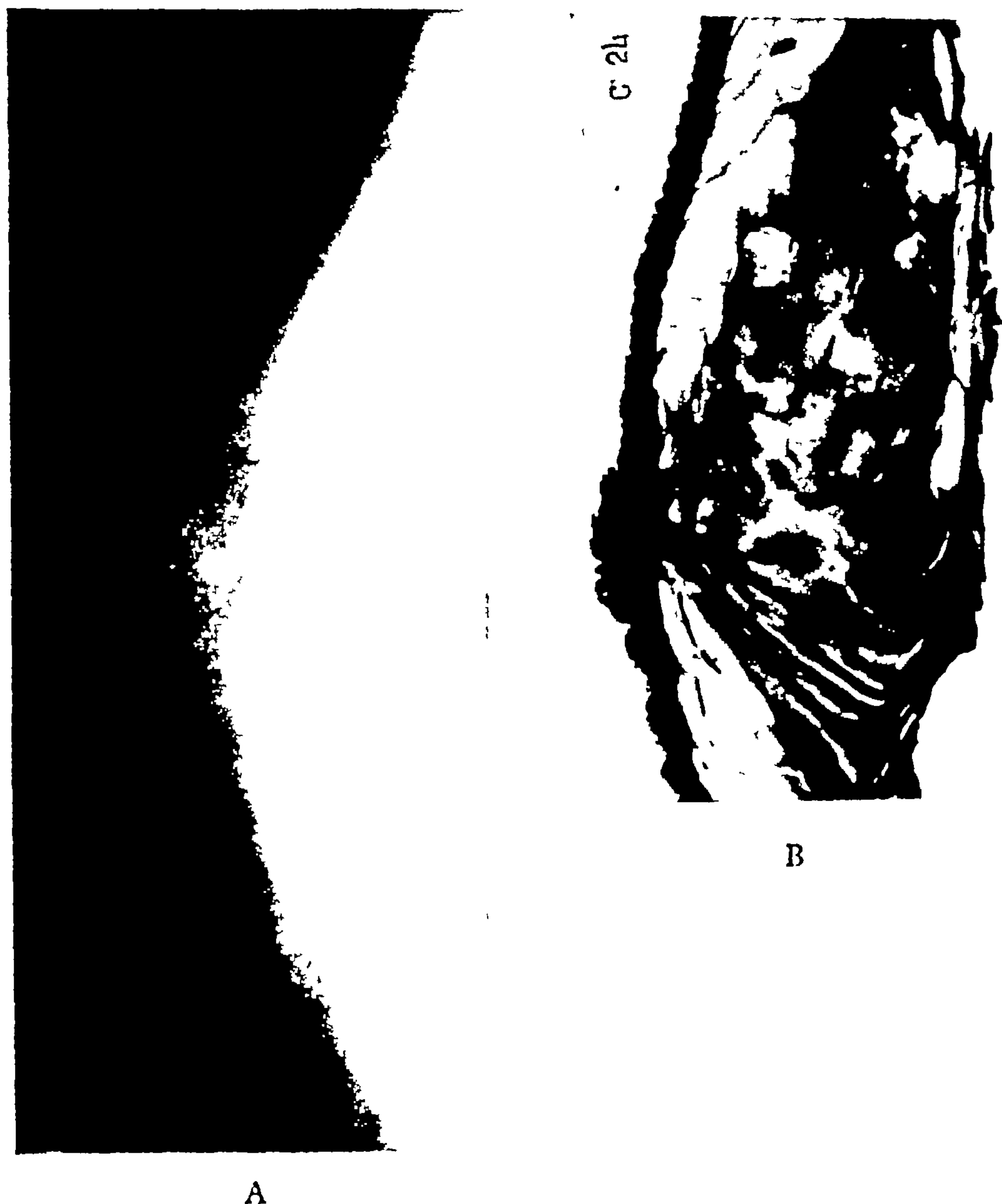


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FIG. 96.

A



B

fibrosa Actually, uncomplicated cases showing only intraductal hyperplasia, epithelial atrophy, and fibroadenomas are unusual. One possible explanation of its pathologic rarity is that Cheatle's mazoplasia does not demand surgery Our verified cases are therefore few Cases diagnosed only on the x-ray film are more numerous, but were not included in our study For pathologic criteria we have relied chiefly on two cases in which simple mastectomy was done. In each, complete serial sections were made and every slice was studied. Except that in one of them there was serous discharge from the nipple, they conformed in every respect to the criteria laid down (figs 94–96) Geschickter noted serous discharge in 4 per cent of his cases of mastodynia, a group which seems to cover mazoplasia fibrosa as well as adenosis In our patient the discharge came from two dilated ducts Apart from a few minute epithelial sprouts which scarcely deserved the name of papilloma, no cause for the secretion was found. However, this woman had undergone hysterectomy ten months previously for myomas The ovaries were left intact, but it is known that hysterectomy per se alters the progesterone metabolism and that cysts of the mammary gland frequently follow the operation. Given dilated ducts at the ampulla, a serous discharge could thus be explained

We believe with Cheatle that the mazoplasia we have been considering is more physiological than pathological. It is seen in a relatively young age group—twenty-five to thirty-five or even younger, and seems to be linked to failure of the adolescent to pass over into the adult type of breast. Young women around the age of twenty often show retarded development of lobules (fig 13A) Some of these cases pass into mazoplasia. Retardation is marked

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FIG 96. C 72. Mazoplasia fibrosa. Age thirty-six years

A. Section through entire breast resembles fig. 95 Part of a dilated duct is seen.

B Same case. Connective tissue stain to show intraductal fibrosis The lumen of the ducts is compressed by a broad collar of fibrous tissue derived from the myothelium. In some places the epithelium has degenerated and all traces of the lumen have disappeared.

by failure of epithelial development. Hence the excess of intraductal tissue. Pregnancy by inducing development of lobules is the best treatment, but unfortunately these women often fail to conceive. When they do give birth to a child, they are seldom able to nurse. We have no direct evidence, but one may hazard a guess that could we examine them, these breasts would belong to Engel's class of hypogalactic glands (fig. 32B).

Apart from pregnancy, any lobules that exist in these breasts are apt to show characteristics of adenosis B. Adenosis of this type often occurs alone, but is also characteristic of mazoplasia cystica One may therefore conclude that a change in hormone balance might convert mazoplasia fibrosa into mazoplasia cystica

MAZOPLASIA CYSTICA

Mazoplasia cystica is a form of dysplasia which combines adenosis and cysts with intraductal fibrosis and often, fibroadenomas. Originally we named it "mazoplasia group II" because study of whole sections showed that increase in intraductal connective tissue is an important and probably fundamental component of this disorder. Fibroadenomas are also characteristic

Mazoplasia cystica has its onset most often in the forties and fifties. The underlying etiologic factor seems to be excess of estrogen with diminution or absence of progesterone. This type of hormone imbalance is sometimes familial or hereditary. It may follow administration of estrogens. Disturbance of progesterone metabolism is known to follow emotional stress, ovariectomy, hysterectomy with or without removal of the ovaries, and thyroid disorders (Cowie and Folley, 1955). In mazoplasia the menstrual cycle often occurs regularly, but the breasts are apt to be excessively swollen and painful premenstrually. Even when regular, the cycle is not a normal one and description of normal cyclic changes based on breasts of this type is apt to be fallacious.

A very large proportion of women with mazoplasia suffer from pelvic disorders including partial or complete sterility In one series of 150 cases which came to operation 72 per cent had pelvic



A B

FIG. 98 C 1215 Mazoplasia cystica. Development of a cyst in an area of adenosis Age thirty-one years Mass left breast two years. Both breasts swollen and tender premenstrually. When first examined a thickened area was detected in the left breast but no mass At the second examination two months later a mass 3 cm in diameter was felt lateral to the areola

A X-ray film on 11/29 54 shows an area of adenosis near the pectoral line Just below this is a very small lobulated opacity (arrow) surrounded by a clear zone This was interpreted as a small fibro-adenoma or cyst





A Fig 98 B

B X ray film on 1/31/55 presents a smooth rounded opacity, interpreted as a cyst, in the area of adenosis Deep to the cyst a faint opacity is just visible, apparently the same tumor as was seen on the first examination.

Operation specimen showed several small cysts The larger cyst had been opened. Adenosis and fibrosis were also present. The small nodule seen in the first x ray film was a fibroadenoma.

A, B Drawings from successive x ray films "cy" cysts— fa" fibroadenoma.

six per cent of the women tried to nurse their children but failed, ten women had caked breasts

The family histories were often significant. Carcinoma of the breast or uterus occurred twelve times in the next of kin. Carcino-

mas in other organs were noted eighteen times, benign breast tumors, twenty-four times. Diabetes was present in the next of kin of nine women out of fifty in which the question was asked, but in the patient herself diabetes is rare. In a series of 1,600 cases we have noted diabetes a few times in dysplasias and carcinomas, but have not had a case associated with mazoplasia cystica. Recently, Scowen and Hadfield (1955) extracted from the urine of normal premenopausal women a nonestrogenic substance which caused marked proliferation of the mammary ducts in male weanling rats. The growth was greater than that induced by 300 mg. of estrone administered over the same period. Extracts of the urine of hypophysectomized women produced no such reaction and it is probable that the substance is of hypophyseal origin. The success which has attended the therapeutic use of small doses of x-rays to the pituitary in certain cases of mazoplasia cystica suggests that this hormone may be a factor in its genesis. Alterations in volume changes in the breasts were measured in two cases and are discussed under this heading.

Many women complain of a sudden onset of pain and the appearance of a mass. This history is too frequent to be ascribed merely to the patient's imagination and we have been able on several occasions to verify the truth of her assertions (fig. 98) Generalized premenstrual pain and swelling is the rule in women with mazoplasia cystica, but in contradistinction to adenosis, variations in the size of the mass are rarely noted Waxing and waning of the tumor is probably due to accompanying adenosis rather than to the cysts themselves. On the whole the cysts tend to increase in size as well as in numbers We have never been able to verify disappearance of a cyst before the menopause otherwise than by evacuation of its contents. We agree with Foote and Stewart (1945) that they are found with diminishing frequency after the menopause and few persist after sixty years of age Cysts in mazoplasia are generally multiple and eventually bilateral They may continue to develop over a period of years and the surgeon is tempted to perform recurrent excisions. In many patients the

histology of the tissue removed during a career punctuated by operations remains the same. A few progress to mastopathy

X-Ray Diagnosis Cysts vary in size from microscopic dimensions to those occupying a large segment of the breast, but only those more than 0 5 cm. in diameter can, as a rule, be seen on an x-ray film. On a satisfactory film, they appear as well-defined opacities with a smooth outline. Isolated simple cysts are usually spherical (fig 106), conglomerate and loculated cysts are either oval or have irregularly scalloped borders (fig 100) As with tumors, cysts are most distinctly visualized on a background of fat. Fortunately for radiologic diagnosis, the majority occur after twenty-five years of age when fat begins to be a normal component of the breast. Their outline can be seen clearly on the x ray film except for those portions which are adjacent to solid parenchyma. There is little difference in the degree of density between cysts and breast parenchyma, but the uniform density of a cyst helps to distinguish it from the trabecular structure of breast tissue. The density of cysts varies somewhat with their contents Bloody fluid or hemosiderin in cysts increases their density A clear space or halo is sometimes seen around cysts as well as around fibroadenomas (figs 99, 102) However, since some circumscribed carcinomas also show a clear peripheral zone, this sign cannot be relied upon for determining diagnosis Nevertheless, careful examination of the margin of the opacity may yield important criteria. Circumscribed carcinomas nearly always show trabeculae or spiculations emerging from the opacity at some point. They must be distinguished from normal breast trabeculae which may overlie or are sometimes pushed aside by the mass Abnormal projections from a carcinoma deviate in shape and pattern from normal markings, as may be demonstrated by comparing them with the contralateral breast, they often cut across the normal trabeculae. A second important distinction is in the type of scalloping of the border Multiple and multilocular cysts show notches at the points of overlap (fig 100) When clearly outlined, the notches are smooth and symmetrical and the description of scalloping is



A

FIG. 99 C 509. Mazoplasia cystica. Age forty-nine years. The breast had always been swollen premenstrually, but no masses were felt by the surgeon or by the patient herself until twelve days ago when she found a large painful mass in the left upper outer quadrant and a similar small tumor centrally in the right breast.

A. The x-ray film presents two sharply outlined opacities (cysts) The

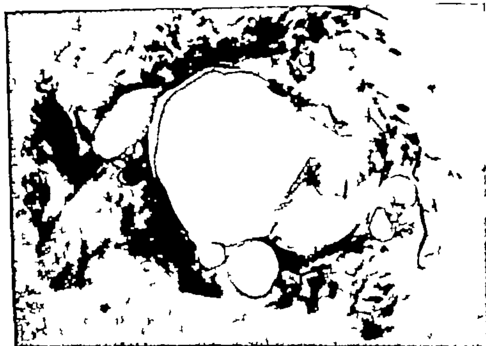


FIG 99 B

larger cyst is overlaid and surrounded by one or two much smaller cysts and by some areas of adenosis The lower edge of it is only faintly visible.

Pathology the operation specimen showed two large cysts containing greenish fluid and a number of small blue dome cysts Between the cysts there were areas of adenosis and dense fibrosis.

B Slicer section showing part of the cystic mass surrounded by areas of adenosis. The cysts are lined by a smooth membrane.

applicable. In carcinoma, notches are seen, but their edges are more or less serrated and irregular and there is nothing symmetrical in their arrangement. The diameter of cysts as measured on the film is usually greater than the diameter measured on the patient In carcinoma the reverse is true.

Multiple cysts are frequently bilateral even when the patient complains about only one breast. In the absence of cysts, adenosis may be expected in the contralateral organ. Vascularity is often considerably increased in mazoplasia cystica, especially in the premenstrual phase. Intermingled with the cysts, fluffy patches of



A

Fig 100 A and B C 878 Mazoplasia cystica. Multiple cysts Age forty-four years Mass in right breast noted six months, tender before periods On examination multiple large and small cysts were felt in both breasts

A. The x-ray film shows multiple, round, sharply defined opacities Since the cysts are superimposed on each other, many are not seen in their entirety A number of them impinge on the subcutaneous

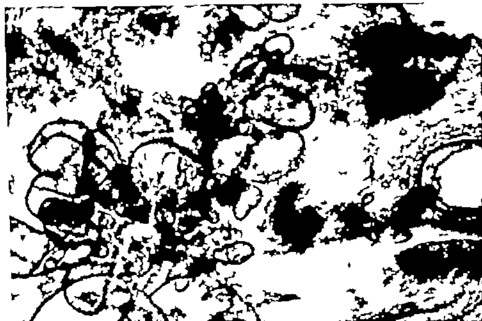


FIG 100 B

fat. The superficial margins are then clearly seen. They present a scalloped outline. In order to demonstrate the scalloped outline in the photographic reproduction, details of the central portion of the breast had to be sacrificed. At operation cysts of all sizes were found, of both mazoplastic and secretory type.

B Slicer section from a somewhat similar case showing multiple cysts of all sizes The patient underwent operations for the same condition eight years and six years previously

adenosis may be seen (fig 99) Solitary cysts are usually unilateral The breast which contains them may reveal no other abnormalities, but often there are signs of adenosis A single cyst of the mazoplastic type is unusual, although they do occur Large apocrine cysts are occasionally seen. Very often a single large cyst is found to be inflamed. If inflammation is at all severe, an origin other than mazoplasia should be thought of A secretory cyst is likely, but if the original lining cells have disappeared exact diagnosis may be impossible. A differential diagnosis between cyst and fibroadenoma cannot always be made on the x-ray film. The point will be discussed under fibroadenoma.

A

B

FIG. 101.

Pathology and Pathogenesis of Cysts The most obvious, if not the most important, features of mazoplasia cystica are the cysts Cysts are common in the breast and differ in their characters according to the type of dysplasia which has engendered them The principal varieties, apart from the common mazoplastic type, are apocrine, secretory, and papillary Pseudocysts are occasionally seen as in some cases of fat necrosis

Apocrine cysts are to be expected since mammary parenchyma and apocrine sweat glands are derived from the same anlage. Small apocrine cysts occur in practically all breasts of women over the age of thirty years and need scarcely be thought of as pathologic. Occasionally a group of them becomes palpable and is removed by the surgeon. In a series of 1,600 cases only one large solitary apocrine cyst was recognized. More may have been present, but large cysts tend to lose their epithelial lining and cannot always be identified. Bunting (1948) made an exhaustive study of these structures and concluded that they were true apocrine sweat glands They were found in normal and pathologic adult women as well as in infants and in a boy of fifteen years The cysts or glands from which they are derived are lined by large pale cells with small nuclei and abundant cytoplasm. Often small papillae project into the cysts The myoepithelial cells are extremely large and well-developed and are similar to those of normally situated apocrine glands (fig 103) Stewart (1950) believes that apocrine cysts may be precancerous He states that 1 per cent of all carcinomas are of apocrine sweat gland origin. We have not been able to trace this sequence in our material

Although secretory disease is characterized by dilatation of ducts, secretory cysts large enough to be clinically obvious are the

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FIG. 101 Comparison of adolescent breast with mazoplasia cystica.

A. Terminal portion of two ducts in a breast from a girl thirteen years old (same case as fig 6) The clubshaped and balloonlike terminal ducts resemble those seen in mazoplasia cystica.

B Mazoplasia cystica in the breast of a woman aged forty five years.

exception rather than the rule (fig. 104). The reason may be sought in the fibrosis, both intra- and periductal, which is ordinarily an important component of the condition The thickened wall is no doubt an obstacle to distention, but, perhaps, even more important, there does not appear to be the same sudden dilatation of a duct in secretory disease as takes place in mazoplasia cystica. Secretory disease in itself is a silent disorder. Pain and swelling of sudden onset indicate plasma cell mastitis, not the formation of a cyst.



FIG 102 C 590 Mazoplasia cystica. Adenosis. Age thirty-seven years Sudden appearance of mass three weeks before X-ray film shows two large cysts (arrows) surrounded by fluffy patches of adenosis.



FIG 103 C 331 Small apocrine cysts from a case of adenosis Age forty four years Paraffin section showing hypertrophy of myothelium. Same case as fig 83

Papillary cysts are easily confused with mazoplasia cystica both clinically and on the x-ray film. The opinion is commonly held that papillomas arise from the wall of a preexisting cyst. It seems more likely that the papilloma has its origin in a duct and that the growth of tumor tissue, together with secretion from the hyperplastic epithelial cells and hemorrhage from broken or degenerated papillae, causes cystic distention of the duct. The subject is discussed in greater detail *in the section on papilloma.*

The cysts of mazoplasia vary in size from 5 mm. to several centimeters in diameter The original epithelial lining is usually atrophic, but slight heaping up of epithelial cells within the lumen is occasionally met with. Provided the cells are typical and differentiation is normal, occasional foci of intracystic or intraductal hyperplasia may be disregarded as far as the diagnosis is concerned Borderline cases in which pathologists may differ in



FIG 104 C 549 Secretory cyst Age fifty-three years Patient presented a rather hard movable mass 3.3 cm. diameter above the areola of the left breast. X-ray film shows a distinctly outlined mass with slight blurring of the edges It is surrounded by a well marked "halo" Pathologic examination showed a secretory cyst with a moderate degree of plasma cell mastitis in the surrounding tissue.

their interpretation are met with here as in all other dysplasias, and the possibility of change in the type of dysplasia has to be thought of. But these exceptions are few, and in practice mazoplasia is easily recognized

The most commonly accepted hypothesis of cyst formation is

that of a blocked duct, but a little reflection will show that this cannot be so The following reasons may be given

1 Cysts are produced by intermittent obstruction. Complete obstruction of an excretory duct causes atrophy of the glandular tissue which it serves

2. Intermittent obstruction of a mammary duct could be brought about by desquamated cells, as postulated by Cheatle. The difficulty arises that in mazoplasia we have never seen enough desquamated cells to cause obstruction. As a rule there are not more than might be seen in a breast at the height of menstruation, they degenerate and are absorbed and they are certainly not enough to block a duct. The theory of obstruction could be more easily invoked in secretory disease which is characterized by abundance of inspissated secretion. But in secretory disease large cysts are unusual and where there is nipple discharge, dilated ducts are found without obstruction. When a dilated duct filled with inspissated secretion and blocked at the nipple is traced back through serial sections to the origin at the periphery of the breast, one finds only a few minute cysts, the remains of the once secreting lobule. Even these seem to be still in communication with the distended duct.

3 Some writers postulate that cysts are formed by the breakdown of partitions between ducts and ductules This mechanism undoubtedly plays its part in inflammatory and degenerative conditions, but can rarely if ever be invoked in mazoplasia cystica Coalescence of cysts may happen at the point of entry of a number of cystic ductules into a larger duct. All are distended. The duct walls are not ruptured, but they are stretched and compressed by pressure of the cyst fluid. They shrink back to form projecting spurs

4. As long ago as 1928, Semb called attention to the relationship which exists between fibroadenomatosis simplex—*our mazoplasia fibrosa*—and fibroadenomatosis cystica mammae, which we speak of as mazoplasia cystica We ourselves soon realized that fibrosis is a fundamental component of both types of dysplasia The

essential difference between the two groups is that in mazoplasia cystica there is hyperplasia with more equal differentiation of basal cells into epithelium and myoid. In mazoplasia fibrosa, hyperplasia is certainly less important, and, judging by the small size of the gland, probably does not occur at all The fault is one of differentiation. In other words there is too much fibrous tissue and not enough epithelium. In mazoplasia cystica, on the other hand, there is failure to maintain definite growing points Instead of new ducts being formed by proliferation of basal cells at certain points only, multiplication of cells involves the entire wall. Differentiation may be normal and the duct will then merely become wider and longer. In the normal adolescent the growing points are at the ends of the ducts and the general elongation causes regular increase in size of the gland. In mazoplasia cystica in certain limited fields there may be close resemblance to the adolescent (fig 101), but in a breast which has attained its definitive development, enlarged ducts cannot elongate and must therefore become tortuous Up to this stage it is likely that no change will have been noted in the breast. But for reasons not clearly understood the duct becomes distended with serous fluid The distention may be gradual, but may be very sudden. We have known it to happen in a matter of hours As the result of distention the duct becomes folded on itself. The lumen may be cut off by a valvelike fold of the wall. The dilated duct is then a cyst Septa, partial or complete, commonly seen in these cysts, represent the remnants of folds (fig 97). In a short time the lining epithelium becomes atrophic and flattened In older cysts it is reduced to a thin membrane. There are no cells from which new epithelium could be generated and certainly no possibility of a secretory function. The intracystic fluid, often under considerable pressure, must therefore be accounted for in some other way. A satisfactory explanation of the phenomenon is at present lacking Hemorrhage cannot be invoked Although slight effusion of blood is common in mazoplastic cysts —the pigment in blue dome varieties is derived from this source— hemorrhage severe enough to have caused obvious distention is

rare and is associated with papilloma rather than mazoplasia. Moreover, blood is by no means universally present and the largest cysts as a rule contain only clear fluid

Consideration of the diameter of a normal mammary duct as compared with the diameter of a cyst makes it obvious that the duct wall must have undergone considerable hyperplasia before its expansion into cysts We have many cases of cysts which appeared following heavy doses of estrogenic hormones Similar cysts are very frequent in women with pelvic disorders known to be associated with hyperestrinization We are therefore justified in postulating that an estrogenic substance is responsible for the hyperplasia which is the primary cause of mazoplastic cysts

We have dwelt at some length on the question of cysts because they are such a prominent feature of the disease and bulk so large in the eye of the surgeon and the consciousness of the patient. Actually, apart from the necessity of differentiating them from other conditions, the large simple cysts of mazoplasia have no importance. Their removal does nothing to prevent cancer and may indeed lull the patient to false security More important is the adenosis which is practically always present and precedes cyst formation. Should operation be performed it is here that the pathologist must look for a possible danger signal In the vast majority of cases of mazoplasia there is good cell differentiation and the myoepithelium is abundant. The adenosis may be of types A, B, and D None is dangerous Only if type C is found, especially if accompanied by intraductal hyperplasia, would there be any question of a precancerous condition. Unfortunately, when cancer does arise in these breasts it is apt to be in areas away from large cysts (fig. 105) The best hope of discovering such cancer in time is by careful x-ray examination.

The size of mazoplastic cysts depends to a great extent on the type of duct affected. Since not every duct becomes cystic, special receptivity on the part of the cells in certain areas has been postulated. Focal alterations in the blood supply, for which a mechanism has been shown to exist, might be responsible. In



Fig. 105





C

FIG 105 C 523. Carcinoma in a cystic breast. Age forty-one years Pain in the left breast two weeks. On examination a mass was discovered centrally and judged to be benign

A. The x ray film shows a large indistinct opacity beneath the marker suggestive of multiple small cysts. In the upper portion of the breast there is a very dense small spiculated opacity characteristic of carcinoma (arrow) This mass could not be palpated clinically

Operation revealed small cysts over most of the breast, and in the upper outer quadrant a carcinoma 1 cm. in diameter Papillomatous proliferation was present in many of the cysts.

B & C. Slicer sections of tumor and cysts.

theory some parts of the breast might be flooded with hormones while other parts are shut off from contact with them. Large cysts most often arise from collecting ducts or their branches, small cysts from lobules or prelobular ducts. In lobules the number and size of the cysts depends on how far the ductules are developed when the abnormal stimulus reaches them. Normally, lengthening and dichotomous branching proceed from definite growing points situated at the distal extremities of the ductules. Stimulation of the entire duct wall would result in expansion in every direction and further branching could not occur. In adenosis B, which is associated with mazoplasia cystica, lobules may be replaced by groups of cystic ducts. The larger the cysts, the fewer their number The inference is that if the stimulus for excessive growth affects the earliest stages of lobular development, there will be no further development of ductules. The few branches already present will form cysts. At a later period of lobular development when terminal ductules are already in being, dilatation may ensue, but will be far less. At this phase of the cycle the proliferative stimulus should have passed its maximum. If it continues, both intraductal and myoepithelial hyperplasia may be expected. As long as cellular differentiation proceeds normally the hyperplasia is not dangerous and will probably end in fibrosis

An all too popular treatment for patients with large cysts is to remove them without taking thought whether operation is the treatment of choice. Assuming that every effort has been made to exclude malignancy the diagnosis should be confirmed by aspiration biopsy. The needle used must not be so large and dull that it will push the cyst aside instead of entering it, nor so small that the cyst contents, especially if they are papillomatous, cannot be withdrawn for pathologic examination Size number 20 is usually suitable If x-ray examination is feasible it is of advantage to check the position of the cyst or cysts with regard to the needle It is useful to verify whether they have collapsed after withdrawal of fluid and to check on the presence of any other lesions which might have been masked by the cyst The injection of an amount

of opaque substance less than the fluid withdrawn has a double advantage It enables a very accurate appraisal to be made of the area drained and by inducing a slight irritation of the cyst lining facilitates occlusion The needle is left in place for a second x-ray examination after the cyst fluid has been withdrawn. An opaque medium is then injected and following a third x-ray study the substance is withdrawn (fig 106) Withdrawal is necessary, otherwise the patient may complain of pain Patients must always be warned that although one cyst may be cured there is no guarantee that other cysts will not form

Aspiration is often curative. If the wall is thin, as in a cyst of recent origin, it will collapse and the cavity is likely to be completely occluded. On the other hand, if fibrosis is present in the surrounding tissue the cyst cannot shrink and will refill in a short time. A second attempt may be made, but if it fails, excision of the area is mandatory The danger of carcinoma in the vicinity of such cysts is a very real one

The fluid must always be collected for pathologic examination. In mazoplasia cystica it is pale or slightly cloudy However, if at some previous time hemorrhage has occurred into the cyst it will be of the blue dome variety and the contents will be greenish black or red, often rather thick. Secretory cysts or abscesses contain grumous material or pus Microscopically on the smear there is usually a heavy precipitate of protein, but the only cells seen are a few degenerated epithelial cells and an occasional lymphocyte. If an intracystic papilloma is present red blood cells and pieces of the growth will be found. The smear will decide whether the tumor is benign or malignant. In either case it must be removed. Occasionally a fibroadenoma is mistaken for a cyst and then of course no fluid will be obtained. The smear may show cells but they will be of a benign type.

Operations are often advised because both patient and surgeon are haunted by the fear of cancer What they fail to realize is that a cancer cannot grow from the atrophic lining cells of large cysts If, as is generally held, mazoplasia cystica predisposes to

B





C

FIG 106 C 334. *Mazoplasia cystica*. Evacuation of cyst. Age forty five years The patient noted a movable mass 6 cm. in diameter above the left areola. She stated that it appeared at 12 a.m. the previous night. On examination a similar smaller mass was found in the right breast X ray examination showed mazoplasia cystica. A needle was inserted into the large cyst and 25 cc. of albuminous fluid withdrawn. A second x ray was taken with the needle in situ. Ten cc. of diodrast were injected into the cavity and a third x ray taken. The diodrast was then evacuated. Pathologic examination of the fluid showed only an occasional degenerated cell.

A. Cyst before evacuation. The indistinct margins are due to surrounding adenosis and small cysts.

B After evacuation.

C. Cyst outlined by diodrast.

malignancy the cancer will arise not in the locality of the cysts but in some other part of the breast. Cysts are often bilateral so that if the bogy of cancer is to be avoided the woman would have to undergo bilateral mastectomy.

What has been said applies to large cysts. If only small cysts are present and they are in great number the prognosis must be more cautious. A mass consisting of closely packed small cysts would give an x-ray picture suggestive of mastopathy rather than mazoplasia. The pathologist would be apt to find small cysts with active intracystic hyperplasia and papillomatosis. Small cysts may be prevalent for one of two reasons: (1) Multiple cystic ductules are typical of adenosis B. (2) Dilatation of prelobular ducts is also characteristic and may be so prominent that it is difficult to decide whether to call the condition adenosis or mazoplasia cystica The question is an academic one. Mazoplasia cystica would imply progression to larger cysts. Adenosis might be stationary or progress to mazoplasia One case of the nonprogressive type came under our notice The woman was operated on twice at three years' interval. The diagnosis on both occasions was mazoplasia, with small cysts and adenosis The cysts were microscopic, and hindsight would point to adenosis rather than mazoplasia Minimal intracystic proliferation is not infrequent in mazoplasia and may be neglected. But where hyperplasia with small cysts is active and progressive, intracystic proliferation may complicate the picture. Multiple intracystic papillomas and groups of actively proliferating epithelial cells are a danger signal. For this reason mazoplasia with small cystic masses should be regarded with more concern than when only large cysts are present.

Fibroadenomas in mazoplasia cystica (fig. 107) may be expected although they are less numerous than in mazoplasia fibrosa and tend to be of a different type. They are formed by coalescence of hyperplastic lobules in the areas of adenosis rather than by overgrowth of intraductal tissue as in mazoplasia *fibrosa* (figs. 111, 112)

Reference has been made to the divergent views of Semb and of Cheatle on the possibility of derivation of mazoplasia cystica



FIG 107 C 491 Mazoplasia cystica with fibroadenoma. Slicer section shows a well circumscribed fibroadenoma lying next to a large smooth-lined cyst. Nearby is an area of adenosis

from mazoplasia fibrosa. The fact that the cystic type appears on an average a decade later than the fibrous type supports Semb's contention. On the other hand, many case histories show gradual onset of mazoplasia fibrosa with increasing pain over the years, whereas the onset in many patients with mazoplasia cystica is sudden with sharp pain which may or may not subside later The fact that cysts are preceded by adenosis might be considered evidence in favor of Cheatle's view, were it not that he includes areas of adenosis in his text figures Settlement of the controversy awaits long-term radiologic studies

FIBROADENOMA

Fibroadenomas have been given many names A few reflect some theory of origin, most are merely descriptive. Since these tumors originate from the mammary parenchyma the term 'adenoma' is

strictly accurate. "Fibro-" understood as an adjective is in order because of the propensity of the myoepithelium to form fibrous tissue.

With a few exceptions fibroadenomas arise during the period of sexual activity. The incidence reaches its peak between twenty-one and twenty-five years of age The chief symptom is the presence of a freely movable mass. In most cases the tumor is solitary, but two or more are not uncommon. Occasionally numbers of tumors up to twelve or more are seen. Pain and tenderness are unusual, but we have seen one large tumor that became exquisitely tender at the time of the menses. The clinical size varies from less than one centimeter to a mass which occupies the entire breast.

Roentgenology. Fibroadenomas consist of tissue resembling that of the normal mammary gland and of about the same density. In the dense breast of young women they are therefore difficult to discern and unless by some device the smooth edge of the mass can be isolated, diagnosis may be impossible. The best way of doing this is to push the tumor toward the surface, using gentle compression of the breast behind it. The capsule then becomes visible against the subcutaneous fat. If possible the examination should be made during the postmenstrual phase when the breast is relatively flabby. The more fat there is, the easier it is to outline the tumor mass The tumor is then seen as a sharply defined, round, ovoid, or slightly bosselated opacity. Often a clear halo is seen around it (fig. 108). Some fibroadenomas are only partly outlined; this means that the mass is only partly encapsulated, a common feature in recent growths. Another exception to the sharp margin is found in menstruating fibroadenomas. Their outlines are often fuzzy due to intense engorgement and edema (fig. 110). Cysts within the tumor as well as mucoid degeneration, seen in so many fibroadenomas, do little to change the x-ray appearance Calcification which is rather common in long-standing tumors of elderly women is readily recognized by its bizarre appearance The particles are large and coarse (fig. 170) They are easily distinguished from the fine grains of calcium seen in carcinomas

and still more easily from the larger and more widespread calcified areas found in late secretory disease and fat necrosis (fig 141)

The differential roentgenologic diagnosis of fibroadenomas would be a simple matter were it not for their close resemblance



FIG 108 C 526 Fibroadenoma. Age thirty-eight years. A sharply defined opacity partly surrounded by a halo is visible deep in the breast. Another small, less well-defined mass (arrow) is visible near the nipple. This could be a patch of adenosis with early transition to fibroadenoma. The fibroadenoma was well encapsulated and had a rather uniform structure of branching ducts lying in abundant stroma.

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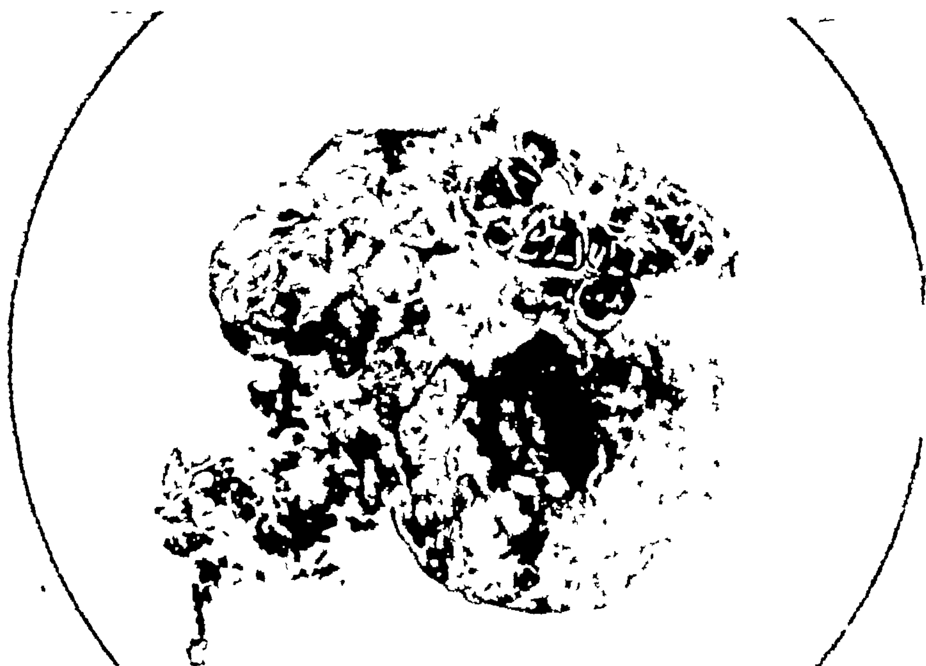
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to cysts Both fibroadenomas and cysts show smooth sharp margins Cysts are apt to be circular, but so are some fibroadenomas A halo is not diagnostic since a clear space occasionally surrounds a cyst. Cysts are more often multiple, but a conglomeration of cysts may mimic a bosselated fibroadenoma. Neither contain trabeculae and if they are large both may show trabeculae displaced to one side by the mass Fibroadenoma is the more likely diagnosis if the breast is that of a young woman, and in practice considerations of age, history, mode of onset, etc., are often helpful.

Fortunately no such difficulty attends the differentiation from carcinoma. Fibroadenomas are quite frequent in breasts with carcinoma, but the distinction between the sharp smooth outline of the fibroadenoma and the spiculated carcinoma is ordinarily very easy to make If difficulty should arise the question may be settled by comparing the measurements of the tumor in the patient and on the film. The measurements of the carcinoma are smaller on the film than in the patient, those of the fibroadenoma are usually larger The rare exceptions to this rule are discussed under the differential diagnosis of carcinoma. Fibroadenoma may accompany other forms of dysplasia. The diagnosis of both conditions can be readily made

The x ray film will often give a clue to the microscopic features which can be expected in a given fibroadenoma A compact tumor with a sharp outline will show as a rule a more or less uniform

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FIG 109 C 148 Giant fibroadenoma. Age forty five years. Mass in right breast two months It increased in size and got larger and firmer at the time of the menses. The tumor occupied the greater part of the gland. It was attached to underlying breast but not to the skin which was red and tense.

A. X ray film shows a homogeneous mass. The margins are well defined but tend to be blurred by the surrounding compressed breast tissue.

B. Slicer section through entire tumor The mass consists of an agglomeration of nodules each of which has a different structure. The tumor is encapsulated except posteriorly where it merges with the breast. Same case as fig 130.

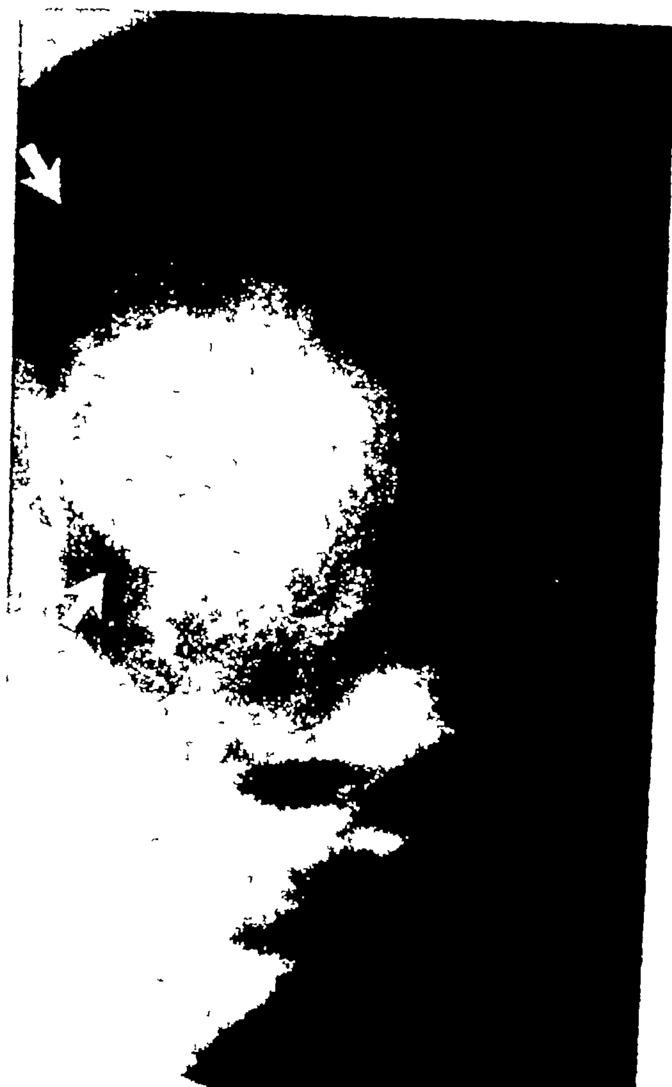


FIG 110 C 556 Fibroadenoma in the menstrual phase. Age twenty-five years. Mass in left breast one year, varied in size When first seen, a large nontender mass was noted in the upper outer quadrant. At the time of operation, one week later, the mass was exquisitely tender The illustration shows a large, rather fuzzy opacity in the upper outer quadrant of the left breast Part of the margins are sharply defined (arrows) Operation revealed an intensely engorged tumor Pathologically the ducts were seen to be distended with shed epithelial cells

structure. An irregular lobulated tumor is likely to be variegated microscopically The state of the breast in which the tumor lies suggests the type of growth which will be found. In mazoplasia fibrosa, or in young women the density of the breast itself makes the tumor hard to see, and one may expect to find a rather uniform pattern with much intraductal fibrous tissue. In older women difficulty in following the outlines of the tumor may be due to adenosis of the surrounding breast. In this case the fibroadenoma may be only partly encapsulated and will probably be variegated Giant tumors may be expected to show considerable variation in structure (fig 109) Calcification is an indication that the tumor is obsolescent and need not be removed.

Pathogenesis Fibroadenomas arise as the result of local irregularities in the cyclic changes of the breast. The hormone imbalance



FIG 111 C 3 Fibroadenomatous lobule in a case of mazoplasia fibrosa. Age thirty three years. Slicer section The increase in size of the lobule is due to intraductal fibrosis. The surrounding connective tissue is pushed aside.



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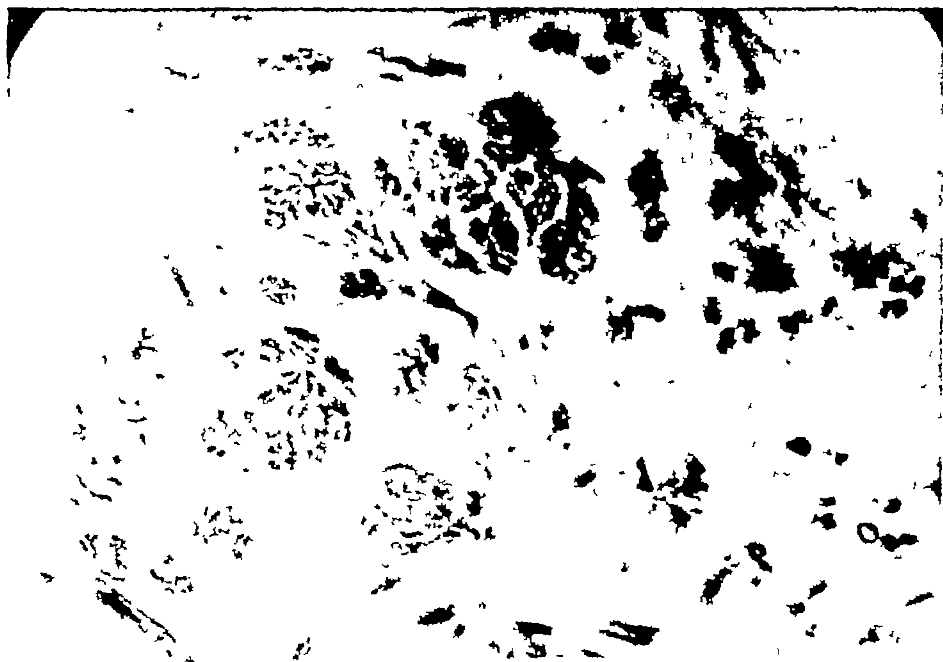


FIG. 112. A

B

of which they are a manifestation is apt to cause some disturbance in the breast as a whole, although later the dysplasia may be limited to one area For this reason the earliest fibroadenomas are seen in conjunction with some other form of mammary dysplasia, sometimes mazoplasia fibrosa (fig 111), or in an unencapsulated area of lobular hyperplasia (adenosis) (fig 112) The rapid growth of the breast at puberty is often attended by foci of irregular proliferation (fig 8) With the termination of the adolescent period most of the irregularities become absorbed into the general lobular pattern of the breast. If abnormal proliferation continues, the surrounding connective tissue becomes compressed and forms a capsule around the area.

Cyclic changes occurring in the rest of the breast are reflected in fibroadenomas albeit imperfectly (figs 113, 114) The changes may occur later and persist longer than in the surrounding normal breast. Alterations characteristic of pregnancy are also seen (fig 115) During pregnancy and lactation some tumors grow rapidly, others, although the epithelium undergoes alteration, show very little over-all increase. Some tumors lactate and secretion may persist in them even after the breast as a whole has returned to the nonpuerperal state (fig 116) After the menopause the fibroadenomatous tissue is often hyalinized and sometimes calcified (fig 117) Rarely, there is an outburst of myoepithelial and epithelial hyperplasia in the tumor and a giant fibroadenoma is formed (fig 137) The majority of giant fibroadenomas occur about the time of the menopause. Such tumors are seldom malignant in spite of the alarming sarcomatous appearance of many under the microscope.

In its earliest stage a fibroadenoma is seen to consist of a small duct and its dependent lobules (fig 118) Most of the lobules

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FIG 112. Incorporation of hyperplastic lobules to form fibroadenoma.

A. Very early stage of process The hyperplastic lobules are pushing the connective tissue aside, but no true capsule is present as yet.

B A clearly outlined area of adenosis A and B A capsule is beginning to form around the mass

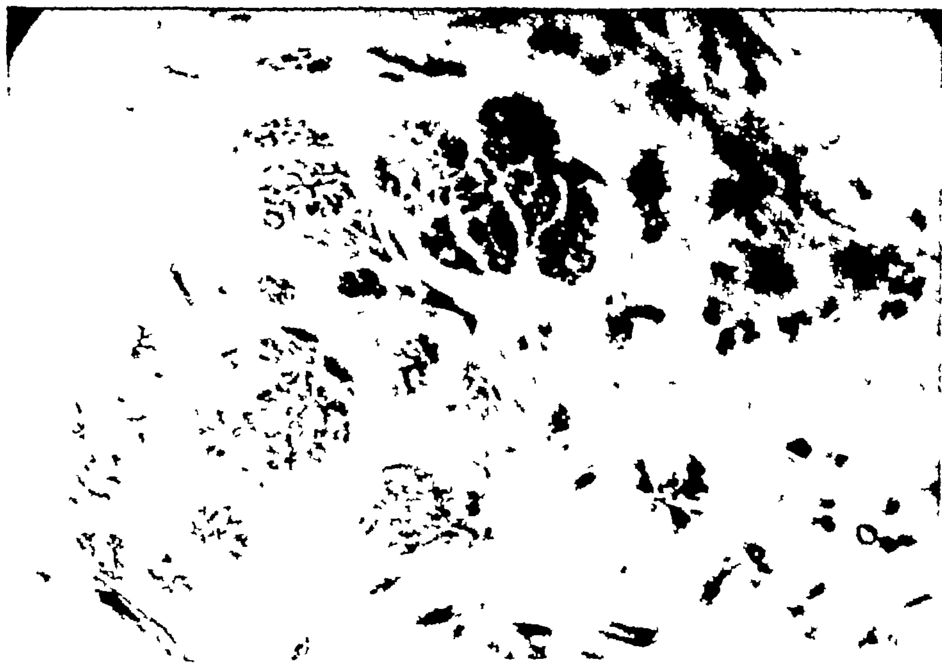


FIG 112. A

B

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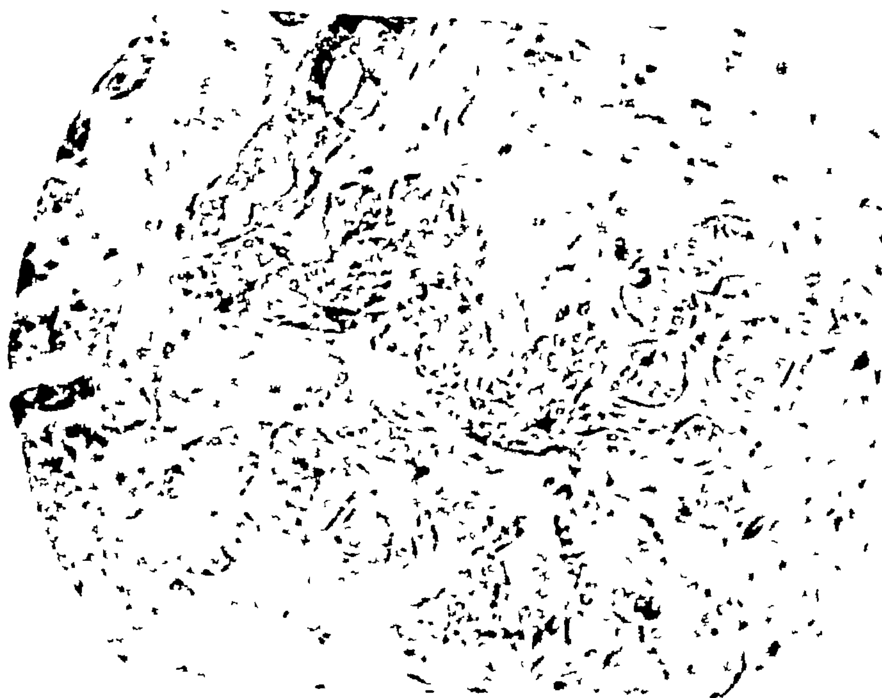
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FIG 113

A



B

show imperfect development, usually due to overgrowth of the intraductal connective tissue Multiple little tumors of this type are very common in mazoplasia. Since most large fibroadenomas are solitary it is evident that regression can and does take place in small growths As the tumor enlarges, the main duct becomes compressed against the capsule and communication with the rest of the breast is lost. It may be this factor which prevents restoration to normal of the affected area. The tumor cells proliferate during the first half of the cycle, but involution which follows menstruation is seldom complete and the mass grows slowly Increase is also brought about by incorporation of adjacent lobules These form fresh nodules which become encapsulated as they grow The older parts of the tumor are usually of the so-called "intracanalicular" type, the recent additions are more likely to be "pericanalicular" Except as descriptive terms these expressions have no significance.

In adenosis the structure is often pericanalicular at first, in contrast to the intracanalicular structure of early tumors in mazoplasia fibrosa (fig 111) This is easily explained by the nature of the two disorders Mazoplasia fibrosa is characterized by overgrowth of intraductal connective tissue. Adenosis is a lobular overgrowth in which epithelium as well as myoid takes part and the balance between the two may be fairly well maintained Cysts in fibroadenomas indicate a uniform proliferation of epithelium along with the myoid, resulting in the formation of epithelial lined cavities Similar cysts occur in mazoplasia cystica. It is possible for a fibroadenoma to grow as a polyp within a duct. This may come about by herniation of the tumor into a duct or by adenomatous proliferation of the duct wall itself Whether the resulting tumor

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FIG 113 Breast and fibroadenoma in the premenstrual phase.

A. Hyperplastic lobule five days before a period.

B Premenstrual proliferation of ducts in a nearby fibroadenoma. The subdivision of ducts is imperfect but the cells lining them are premenstrual in character

FIG 114

A

B



FIG 115 Multiple fibroadenomas showing hyperplasia due to early pregnancy Budding of ducts is seen in all parts of the tumors (slicer section)

is an adenoma or a fibroadenoma will depend on the proportion of myoid to duct epithelium The intraductal tumor may be predominantly papilloma, adenoma, fibroadenoma, or the kind called sclerosing adenosis by Urban and Adair Any or all of these forms may likewise be found within a cystic duct which is part of a fibroadenoma

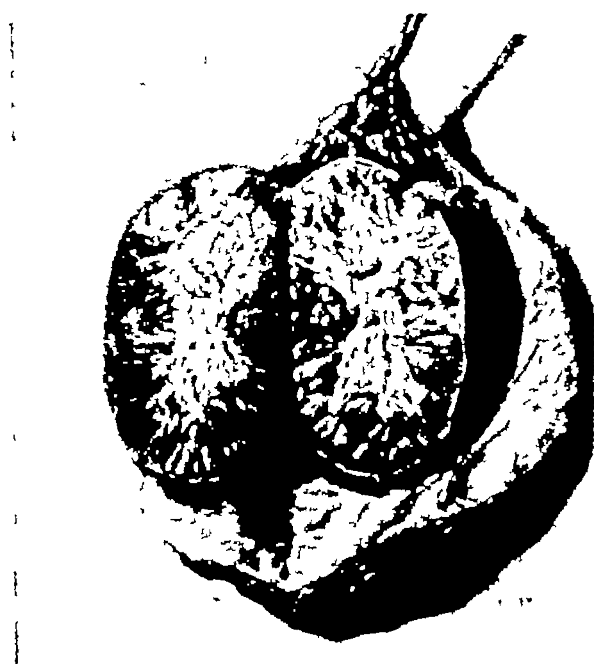
Authors have tried to classify fibroadenomas according to their histologic appearance, but detailed classification such as this implies has few if any uses and may erect barriers where none exist. Most fibroadenomas are formed of a conglomeration of encapsulated nodules which may present characters very different from each

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FIG 114. Paraffin sections of breast and fibroadenoma, three days after onset of menstruation. Both show massive epithelial desquamation. The epithelial changes in both are similar The breast (A) contains some lobular structures, not seen in the fibroadenoma (B)

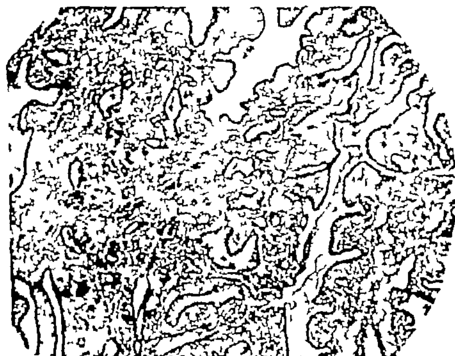


FIG 116. A



B

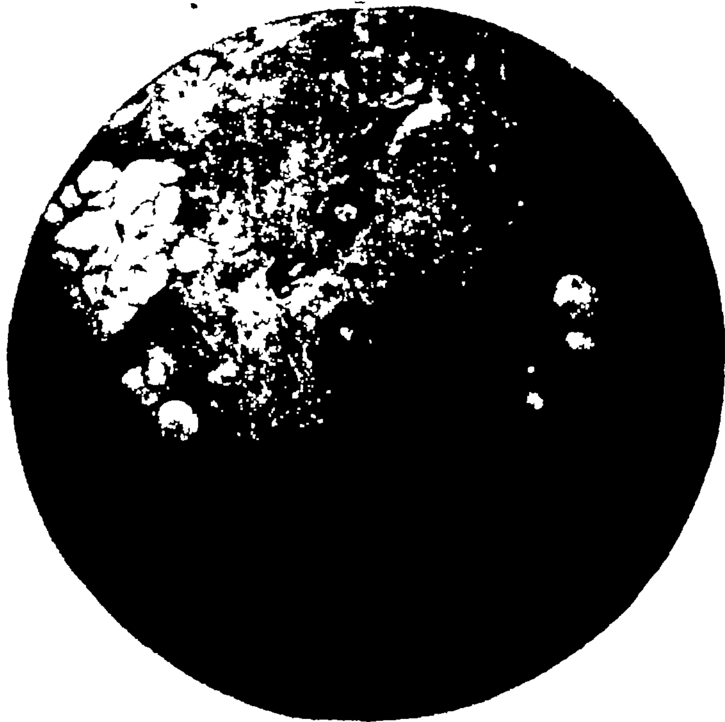
other This is not surprising in view of the variability of the breast lobules in one and the same organ, a variability which is exaggerated in fibroadenomas Those that arise in breasts with mazoplasia fibrosa may show a simple structure to begin with, but variations due to proliferation in one area rather than another soon make their appearance. The differences in architecture that may be seen in an early tumor are shown in fig 118 The tumor consisted of one



C

FIG 116 Lactating fibroadenoma. M.F, age eighteen years After delivery of her first child ten months previously she had a painful swelling in the left breast which gradually increased in size. She did not nurse. At operation a smooth encapsulated mass occupied the greater part of the breast. Microscopically the tumor consisted of dilated ducts lined by secreting cells The intervening tissue showed characteristic lactation involution together with groups of actively secreting acini.

A. Before operation.
B. Operation specimen.
C. Paraffin section of tumor ×50



A

Fig. 117



B



FIG 118 Small fibroadenoma arising in a case of mazoplasia cystica. N.D., age forty two years. The tumor is formed by a small dilated duct and its branches. Each branch shows a different pattern of abnormal proliferation.

duct and its branches To make a separate classification for each of the types shown would obviously be absurd. In tumors which originate in areas of adenosis, variations are present from the start and are even more accentuated when aggregations of abnormal lobules are added to the original mass Each part of a tumor may proliferate in a different way In one and the same tumor the lesions of mazoplasia cystica and fibrosa, adenosis types A, B, and D, intraductal hyperplasia, papillomatosis, and myoid hyperplasia with fibrosis may all be represented. To add to the confusion, normal cyclic changes may be expected, these are most in evidence

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FIG 117 Postmenopausal breast and fibroadenoma.

A. Atrophic breast.

B Fibroadenoma showing atrophy of epithelium and hyalinization of stroma.

COMPARISON OF A TYPICAL BENIGN CANINE FIBROADENOMA WITH HOMOLOGOUS TUMORS IN WOMEN (FIGS. 119–132)



FIG 119 Giant fibroadenoma in a cocker spaniel bitch Slicer section shows considerable variations in different parts of the tumor.

at the periphery of the tumor. Besides proliferation, degenerative changes are present in all but very recent tumors. Edema and mucoid degeneration, hyalinization, and calcification are common Epithelial necrosis occurs in massive shedding sometimes associated with menstruating tumors. Larger areas of necrosis result from sudden interference with the blood supply. Adipose tissue may be included in a fibroadenoma, but actual fatty degeneration is unusual. Fat is present in lactating tumors and minute fat droplets are occasionally found in the epithelium in the premenstrual phase and during pregnancy.

Bizarre features, occasionally met with in human mammary tumors, have misled observers into coining names such as chondroma, osteochondromyxoma, etc, thereby implying a different type of growth and harking back to the so-called "mixed" salivary gland tumors of the older pathologists Of course salivary

gland tumors and myothelial mammary growths have much in common. But for interpretation of unusual forms of fibroadenoma in women the best method is to begin by a study of tumors in canines

Benign mammary tumors in the bitch are important because they show much greater variation of structure than do those of the human female. In bitches pseudocyesis is common and often recurrent. Swelling of the breasts is present and lactation is apt to follow the false pregnancy The disturbance in mammary tissue often results in tumors These may be multiple in several breasts and the giant type is not uncommon As in humans, malignant change is rather rare, although the varied and bizarre appearance of these growths may mislead the observer

The following description of a typical benign canine tumor exemplifies the distortions of which mammary tissue is capable The growth was from a cocker spaniel bitch and measured



FIG. 120 C 148 Giant fibroadenoma in woman. Slicer section from the same case as fig 109, shows an aggregation of lobules which vary greatly in their architecture. Cysts filled with intracystic papillomas are seen in the upper left hand corner



FIG 121. Fibroadenoma in spaniel Nodule containing numerous epithelial lined tumors. Note papilloma in upper left hand corner.

12×6×7 cm A nipple projected from the skin surface. On section the mass was partly solid, partly cystic (fig. 119). It consisted of nodules, some of which were hard and fibrous, some softer and congested.

Microscopically the tumor nodules varied considerably in structure among themselves. Many presented tubules lined with epithelium and some of these contained secretion (fig. 123). All of them were surrounded by abundance of myothelial cells and fibers. Myothelial cells were often found impinging on the lumen of the duct and in some nodules they replaced the epithelial cells. Epithelial cells, if they had ever existed, had disappeared (fig 125)

The ducts themselves varied considerably in size In some places they formed large cysts which were partly filled with secretion, sometimes with necrotic material. Inflammatory cells were present in the secretion in several of the cysts The general pattern of these cysts resembled that seen in cystosarcoma phyllodes

The tumor, of enormous size when one considers the dimensions of the animal which carried it, would seem at first sight to have little in common with human fibroadenomas Yet a review of the slides from fibroadenomas in our series showed many areas in different tumors which paralleled one or more features in the spaniel. The advantage of studying canines is that they present as it were a diagram of many features that are difficult to evaluate in women. The behavior of the myoepithelium in particular is so clear that it may be used as a guide to follow the growth of human tumors

This method of interpretation is made plain if the illustrations from the canine tumor are compared with those taken from human fibroadenomas Fig 120, the same tumor as fig 109, is from a woman forty-five years old. The lobulated mass shown on the x ray film was of a variegated type, as revealed by the slicer sections The paraffin section presented distorted ducts with very active



FIG 122. Giant fibroadenoma in spaniel Lactation involution following pseudocyesis Compare with fig 124.

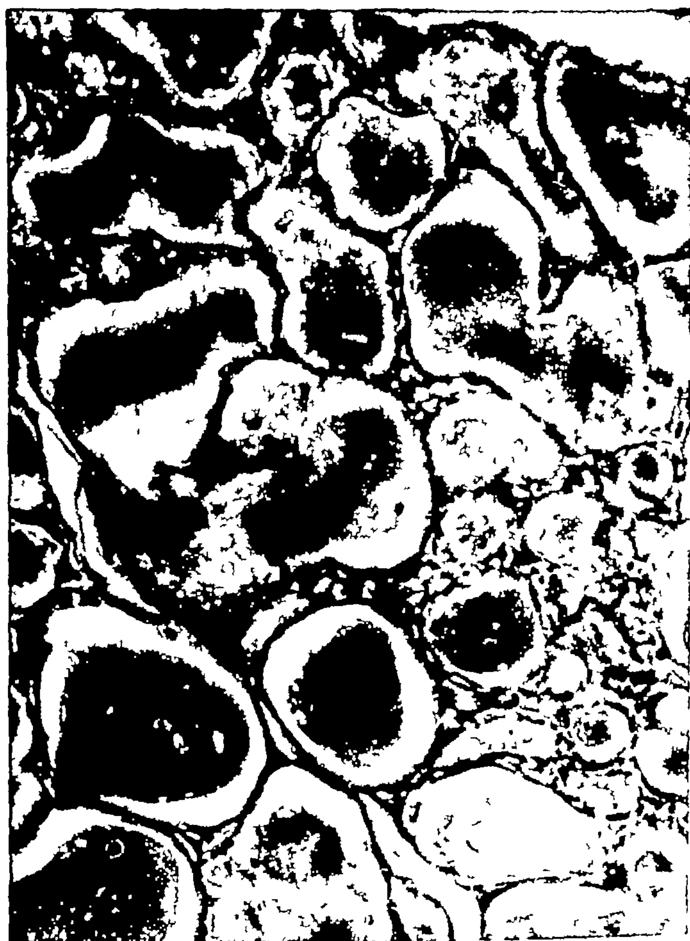


FIG. 123 Spaniel. Residual lactation acini in fibroadenoma following pseudocyesis The acinar walls are lined by flattened cells in contrast to the projecting cells capped by globules of secretion which are seen in the woman, fig. 124 Secretion in the spaniel is inspissated and is no longer in contact with the acinar walls.

myoid proliferation, surrounded by a broad zone of mucoid degeneration Close to the ducts were a number of faintly outlined degenerating myoid nuclei in which a "foam" pattern could be discerned. A proliferation of this type is seen in fig. 130. The nuclei were very similar to those described originally by Peyron and Brugnatelli in early pregnancy. Peyron called them histiocytes, but in our sections we can find all transitions between Peyron's cells and the myoid. In our bitch tumor, mucoid degeneration was

present in only a few nodules In these areas similar nuclei were identified.

Figure 124 is an example of a lactating fibroadenoma in a woman who had ceased nursing for four weeks Microscopically the tumor presented greatly dilated ducts which in the fresh specimen were distended with milk. The pattern of the ducts was the same as in the spaniel, but in the spaniel the acini were no longer actively secreting (figs 122, 123)

Myoepithelial development is exemplified in figs 126 and 129 In the first case, a woman of forty-six years had mastopathy with considerable fibrosis and multiple fibroadenomas which showed all stages of development from very early formation to atrophy and calcification. Some ducts were lined only by myoepithelium. Fibrils from the myoid cells merged with the surrounding fibrous tissue which was very dense. Here and there rows of myoid nuclei indicated the site of former ducts Exactly the same process was seen in the spaniel (figs 125, 127), but the development of the

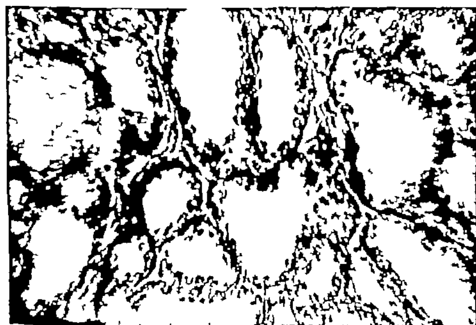


FIG 124. Lactation in a fibroadenoma from a woman seven weeks post partum. She had ceased nursing four weeks before.



FIG. 125. Spaniel. Section shows ducts lined only by myothelium. The myothelial cells are irregular and some show fibrillary processes Elongated nuclei resembling those of fibrocytes but actually derived from the myoepithelial cells are seen in the surrounding tissue.

myoid was more even and the fibrous tissue was not as dense. In the spaniel there was marked "pallisading" of the myoid cells due to retention of their original pattern of proliferation around the lumen of the duct (fig 127). Traces of pallisading could also be seen in the tumor shown in fig. 126 and other human tumors. The second case (fig. 129, the fibroadenoma pictured in fig. 137) shows mucoid degeneration of myothelial cells in a rapidly growing tumor. It may be compared with fig. 128 presenting a similar formation in the bitch. Both contained areas where duct epithelium had almost disappeared and was replaced by myothelial cells. Areas of sclerosing adenosis (myoid sclerosis) are seen in the spaniel and are not uncommon in the fibroadenomas of women; compare figs 131 and 132. Intraductal papillomas found in the bitch did not differ from those that are frequent in human giant fibroadenomas (fig. 121).

Carcinoma is hardly ever discovered arising in a fibroadenoma Yet carcinomatous breasts frequently contain one or more fibroadenomas Geschickter gives evidence indicating that carcinoma is twice as common in women operated on for fibroadenomas Here we are dealing with two separate things (a) the liability of fibroadenoma to undergo carcinomatous change, (b) the liability of a breast affected with a form of dysplasia which left fibroadenomas in its wake to develop carcinoma subsequently With regard to (a), it will be recalled that the principal components of a fibroadenoma are myoepithelial cells The immature form of these cells is very rarely seen in carcinoma, so rarely that their absence may be used to confirm the impression of malignancy in doubtful cases Proliferation of epithelial cells is seen occasionally in fibro-

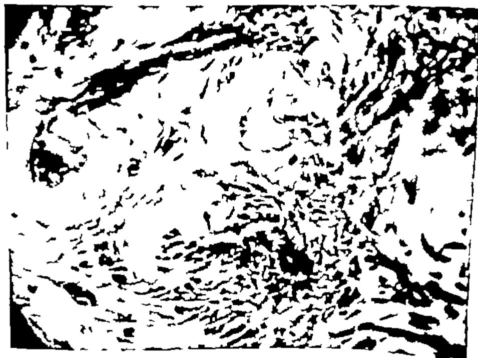


FIG 126 C 94. Fibroadenoma in woman. Age forty-six years Case of mastopathy, with multiple fibroadenomas, illustration shows a fibroadenoma with ducts lined only by myoid cells which are in process of forming dense fibrous stroma. In some places rows of myoid cells indicate the site of former ducts.



FIG 127 Giant fibroadenoma in spaniel, to show pallisading of myoid cells The rows of myoid nuclei indicate the site of former ducts.

adenomas and accompanies hyperplasia of the tumor as a whole. But even in large and active tumors there is a strong tendency for differentiation to myothelium rather than epithelium With regard to (b), the situation is otherwise. Fibroadenomas arise in dysplastic breasts, more specifically in dysplasias where excessive estrogen stimulation is at work. Estrogens, though not a cause of cancer, are one necessary precursor of malignant disease in the breast (Lacassagne, 1932). True, factors other than estrogen stimulation must be at work before carcinoma can arise; still, one may assume

that in breasts with fibroadenomas the groundwork for future malignancy has been laid

Sarcomas, while rare, originate in fibroadenomas more frequently than in other breast structures Perhaps "sarcoma' is a misnomer since the tumor arises from immature myoepithelial cells But as these produce the fibrous stroma of the benign form and the word conveys a mental picture of the type of malignancy, it may as well stand. The differential diagnosis between sarcoma and giant fibroadenoma (cystosarcoma phyllodes) is often difficult. Sudden growth accompanied by pain in a fibroadenoma which has been quiescent for years should arouse suspicion Microscopically, if the pathologist is lucky, he may see numbers of large atypical nuclei and perhaps mitoses Normal myoepithelial cells do not exhibit mitoses Large areas of necrosis point to sarcoma. Increased

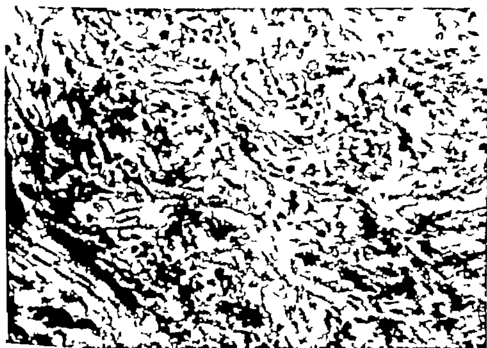


FIG 128 Giant fibroadenoma in spaniel. A few small ducts are lined only by myoepithelium. Elsewhere the ducts are replaced by rows of myoid cells. Mucoid degeneration is seen in the stroma

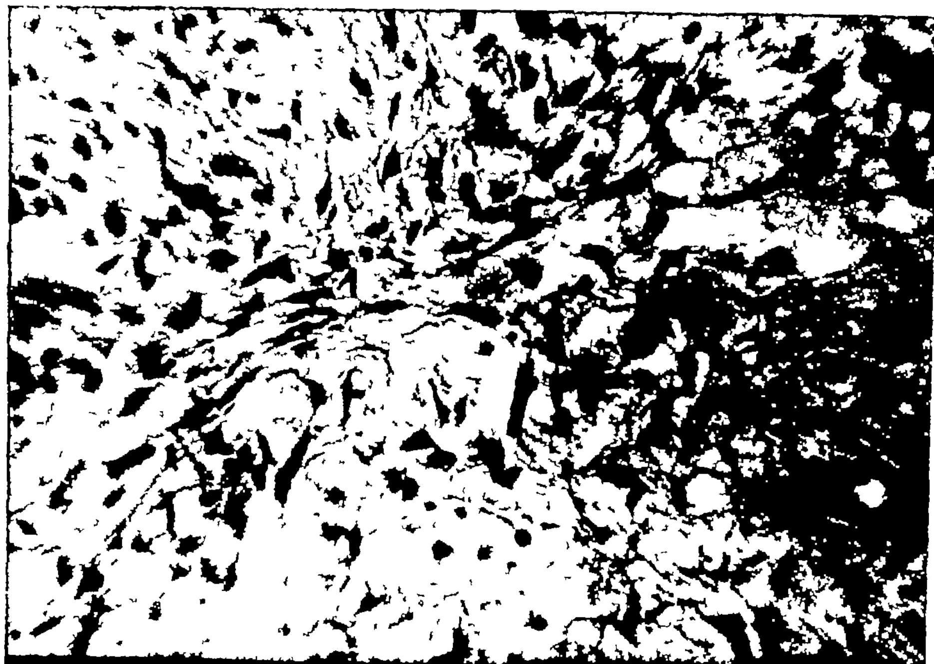


FIG. 129. C 163. Giant fibroadenoma in a woman aged fifty-three years, same case as fig. 137
In the center a duct has been replaced by myoid An earlier stage of the same process is seen in the small duct near the lower right margin of the illustration The stroma consists of stellate cells, the result of mucoid degeneration.

vascularity is not in itself diagnostic, but in sarcoma the vessels may be lined only by tumor cells.

The Myoepithelium in Fibroadenomatous Tumors. From early times the connection of fibroadenomas with the myoepithelium had been suspected, but Peyron (1924, 1926) was the first to describe the part played by these cells in tumors of the bitch, mare, and cat. Because of the peculiar combinations found in canine tumors it has taken a long time for Peyron's observations to be assimilated by writers on human pathology. In 1931 Gaudier and Lambert diagnosed as myoepithelial a mammary tumor which resembled that seen in bitches, but their paper does not seem to have aroused much interest. In 1932 Melnick described a fibromyoma in a woman. He suggested the possibility of a myoepi-

thelial origin but passed it up in favor of derivation from the smooth muscle of the nipple ducts Hamperl describes the myoid in human fibroadenomas, although he hesitates to go all the way in ascribing the entire stroma of these tumors to the myoid. Kuzma

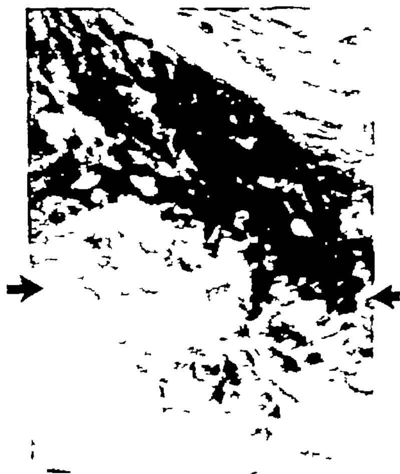


FIG 130. C297 Myoid proliferation in a giant fibroadenoma. Woman aged forty three years. Myoepithelial cells arise from the hyperplastic basal layer and stream outwards (arrow). Note vacuolated nuclei of the degenerated myoid cells in the adjacent intraductal tissue. This part of the tumor showed marked mucoid degenerati (arrow)



FIG 131 Giant fibroadenoma in spaniel. Myoepithelium resem
that seen in sclerosing adenosis Shows elongated fibrils sepa
by rows of dark nuclei, a formation common in sclerosing adenos

follows Hamperl in this. Capone-Braga and Bartolini (1945), i
exhaustive study, coordinated the findings in a series of malig
"mixed" tumors of bitches with similar tumors in women. T
traced the genesis of cartilagenous nodules as well as of the fib
stroma to the myoepithelial cells. Later Rosemary Biggs reinfo
their findings.

The nature of fibroadenomatous tumors is revealed by deta
cellular study. It had always been assumed that the fibrous str
of a fibroadenoma was a fibroblastic reaction of cells derived fr

the mesoblast. This assumption was challenged by Peyron With reference to a fibroadenoma in a bitch he pointed out that the basement membrane of the ducts is formed by myoepithelial elements He then described the growth of hyperplastic myoepithelium outward from the wall. We quote "Once these zones of proliferation are isolated from the ducts they become progressively incorporated into the primitive stroma of the tumor" Again "The external layer rapidly loses its myoepithelial character to undergo an evolution into fibrillary reticulum. The process is identical with that described by the author and Masson in mixed salivary gland tumors" Peyron traced the transition of intracellular myoepithelial fibers to precollagen, then to collagen. The cellular elements reduced to their exoplasm become fusiform and resemble fibroblasts Peyron's findings agree in every respect with our own independent observations on the behavior of the myoid in women.

Myoepithelial hyperplasia takes part in many pathologic

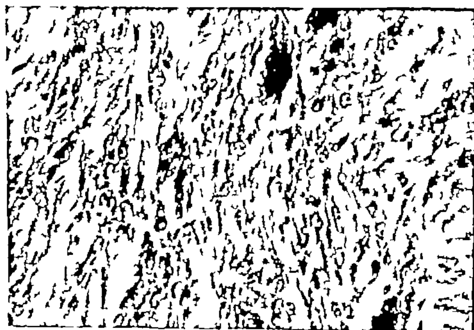


FIG 132. C 989 Extensive sclerosing adenosis in a fibroadenoma. Woman aged forty years.



FIG 133. C 3. Fibroadenoma Early stage of *myoepithelial proliferation in the wall of a duct*

processes both in benign hyperplasias of the mammary gland and in the reaction to malignant disease; it is a possible precursor of sarcoma. The first stage is multiplication of the undifferentiated basal cells. What becomes of these depends largely on environment. They may differentiate into epithelial cells which reach their ultimate normal development in lactation or, abnormally, in its parody, secretory disease Alternatively they form myoepithelium

Basal cells which remain immature may degenerate, but should their proliferation be continued they are likely to form a focus of carcinoma. The recognition of differentiated myoid cells is extremely important because any lesion which shows them in large numbers is almost certainly not carcinoma.

The growth and development of myoepithelial cells has been described in pregnancy Under pathologic conditions hyperplasia



FIG 134. C 837 Myoepithelial proliferation in fibroadenoma. Age thirty four years Mass 1 8 cm. diameter just below left areola. Operation revealed a very small aggregation of fibroadenomatous nodules. Paraffin sections showed active proliferation with marked myoepithelial hyperplasia.

scussed by Rodman and Ingleby in 1939, by Tice in 1948, and stated by Haagenson in 1950. In recent years roentgenographic udies combined with serial sections of entire glands have estab-hed that secretory disease and plasma cell mastitis are one noso-gical entity and clarified much that was previously obscure.

Although secretory disease is the direct cause of chemical astitis, better known as plasma cell mastitis, it is never inflam-atory in its inception and may run its entire course without flammatory complications. The term "comedo mastitis" is erefore incorrect and moreover substitutes a purely descriptive rm for an etiologic cognomen. Originally we spoke of secretory stic disease, later we realized that although cysts occur, the ducts e often uniformly dilated rather than strictly cystic. As in mazo-asia cystica the cysts are not fundamental, they are secondary to perplasia of all the components of the duct wall. Secretory sease may engraft on any of the dysplasias and is rather equently seen with mazoplasia cystica.

In secretory disease distention of the lumen by products of cretion is a prominent feature. Here, if anywhere, blocking of e ducts by thick, inspissated secretion might be plausibly in-ked to account for the dilated ducts and the occasional cysts. it when it is recalled that the more numerous and larger cysts mazoplasia cystica are filled by relatively thin, acellular serous iid and the dilated ducts of secretory disease are often not ocked, but discharge their contents via the nipple, it is obvious at the theory will not hold Actually in secretory disease there is oliferation of both epi- and myothelium. The proliferation is llowed by differentiation of the epithelium into secretory cells d the myothelium into fibrous tissue. Because of more complete fferentiation, cell proliferation ceases sooner than in mazoplasia ence there is less growth of the duct wall, the dilatation of the men is never as great as in advanced cases of mazoplasia cystica, d cysts are not formed to the same extent

X-ray studies have shown that secretory disease is nearly always lateral. In the absence of complications many patients are

asymptomatic. The disorder may be an accidental finding at autopsy It is occasionally discovered on an x-ray film during investigation of some other breast condition The inference is that secretory disease is not in itself harmful Symptoms, when they appear, are generally unilateral and the majority of clinical cases show at least minimal plasma cell mastitis For clinical purposes therefore the disorder and its complications may be discussed together

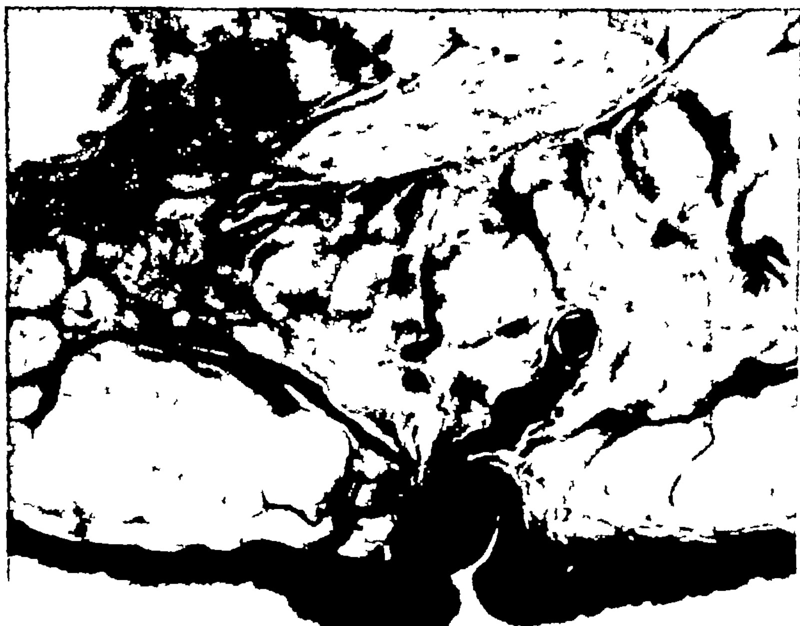
The history differs in many respects from that which obtains in other forms of dysplasia The age of onset is difficult to determine because manifestations may only show themselves after years of quiescence. When symptoms do appear the patient is usually alarmed and seeks advice promptly The age at which symptoms are discovered averages forty-seven years, but varies from the early twenties to the seventies Once established the disorder continues indefinitely Nearly all cases occur in married women. In our series only eight out of seventy-one were single. In contradistinction to mazoplasia, the women who desired children had larger families than the average. Most women nursed successfully, but 15 per cent had had puerperal mastitis A few gave a history of cracked nipple. A history of pelvic disorders was elicited in 22 per cent as against 80 per cent of cases of mazoplasia.

The chief symptoms in the order of their diagnostic importance are nipple discharge, nipple retraction, tumor, and pain. The first two are seldom present together because the fibrosis which causes retraction is apt to compress the ducts beneath the nipple and block the exit of secretion. Either may be unilateral or bilateral

Nipple discharge occurs in about 40 per cent of cases as compared with 5 per cent of nipple retraction. Secretion may be intermittent or continuous In uncomplicated cases in young women the discharge resembles milk. Some patients give a history of recrudescence of lactation after they had stopped nursing Usually the secretion ceased, to return months or years later Pregnancy is not a necessary factor Lactation in virgin breasts is a well known although rare clinical phenomenon. It has been produced experi-



A



B

Fig. 138

mentally in animals by exhibition of suitable hormones None of our unmarried women had a milky discharge, but one case in a young woman who had been married a few months and was not pregnant has come under our notice. In older women the discharge is thick or inspissated and is apt to be discolored gray or yellow Occasionally a serous or even frankly bloody discharge is seen, but repeated examination reveals the usual opaque secretion. In plasma cell mastitis it is reddish brown, green, or even black. The colors are due to degenerated blood which oozes from ulcerated surfaces in the ducts Bright red discharge is unusual.

Retraction of the nipple takes place gradually over a longer period of time than is the rule in carcinoma (fig 138) A history of two years is not uncommon and no tumor commensurate with a malignant growth of that duration can be palpated. Bilateral retraction when not congenital is strongly indicative of secretory disease.

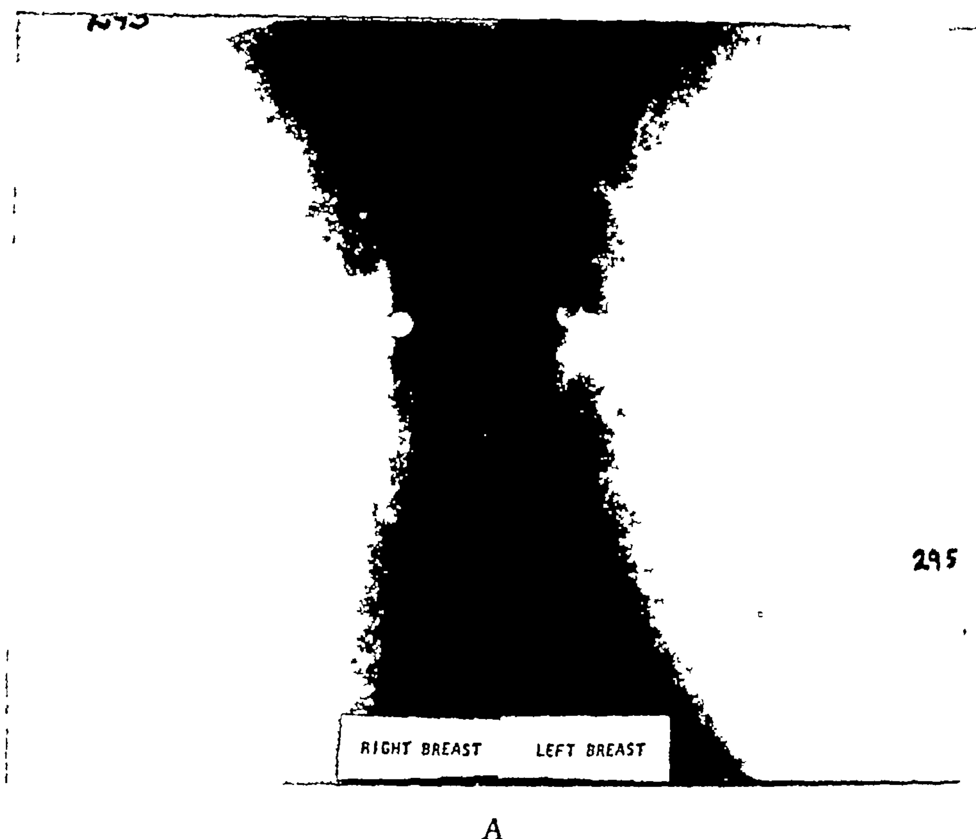
A tumorlike mass is palpable in about half the cases The affected area is often not definite enough to be called a tumor More commonly dilated ducts can be felt beneath the nipple. The tumors of plasma cell mastitis may be soft or hard Their outline is often indefinite. They are usually tender, pain often increases in the premenstrual phase. In the earliest stages of the inflammatory process the skin may be reddened or discolored. The commonest site for the masses is in the subareolar region, but they

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FIG 138 C 372 Secretory disease with marked nipple retraction. Age fifty-eight years Gradual retraction of the right nipple for two years On examination the apex of the right nipple lay in a depression 0 5 cm. in depth. Dilated ducts could be palpated in the subjacent tissue. The left nipple was only slightly retracted.

A. X-ray film right breast. The nipple lies in a depression and is almost covered by folds from the adjacent areola. The breast itself is fibrous and presents two systems of dilated ducts (arrows).

B Slicer section The nipple is retracted. Dilated ducts filled with grumous material are seen beneath it. Similar ducts were seen throughout the series cut. They could be traced to small cysts at the periphery of the breast.



A

FIG. 139. C 295 Secretory disease and plasma cell mastitis The patient aged forty-six years complained of a soft painful mass 1.5 cm in diameter beneath the right nipple It had been present one week. The nipple was retracted and inflamed and a thick discharge could be squeezed from it. No discharge was present on the left side, but the nipple was also retracted

A The x-ray films show bilaterally retracted nipples with thickened areolae The dilated ducts beneath the right nipple are seen as a single mass, resembling the stem of a torch which has flamelike extensions fading out toward the base of the breast. At the junction of the stem and flames of the torch is an indefinite mass of homo-

may be found in the upper outer quadrant or elsewhere The inflamed patches may occupy the greater part of the breast or may be too small to be detected clinically Although a mass may be palpated in only one breast, the x-ray film sometimes shows that both are involved in the inflammatory process.



FIG 139 B

geneous density resembling a patch of lactating tissue, characteristic of plasma cell mastitis This is distinct from carcinoma because the fine spicules of malignant infiltration are lacking, also the tumor was larger on the x ray film than by palpation. The left breast reveals a lesion similar to that in the right breast but less advanced and lacks the tumorlike infiltrations of plasma cell mastitis

B Paraffin section secretory disease and plasma cell mastitis (a) necrotic duct, (b) degenerating colostrum cells in epithelium of adjacent larger duct, (c) degenerated secretion in large duct not as yet involved in the inflammatory process. Note secretory cells in the lining epithelium.

Pain is not characteristic of secretory disease per se, although a few women complain of drawing sensation and bilateral fullness which is relieved by nipple discharge. Pain is generally an indication that plasma cell mastitis has supervened. A very typical history is one of slight trauma, insufficient to cause damage in a



A

FIG. 140 C 3002 Secretory disease. Plasma cell mastitis. Age sixty years. Sudden onset with pain, redness and swelling One week later the pain and redness had subsided and the swelling had diminished An irregular, freely movable, nontender nodule was now palpated.

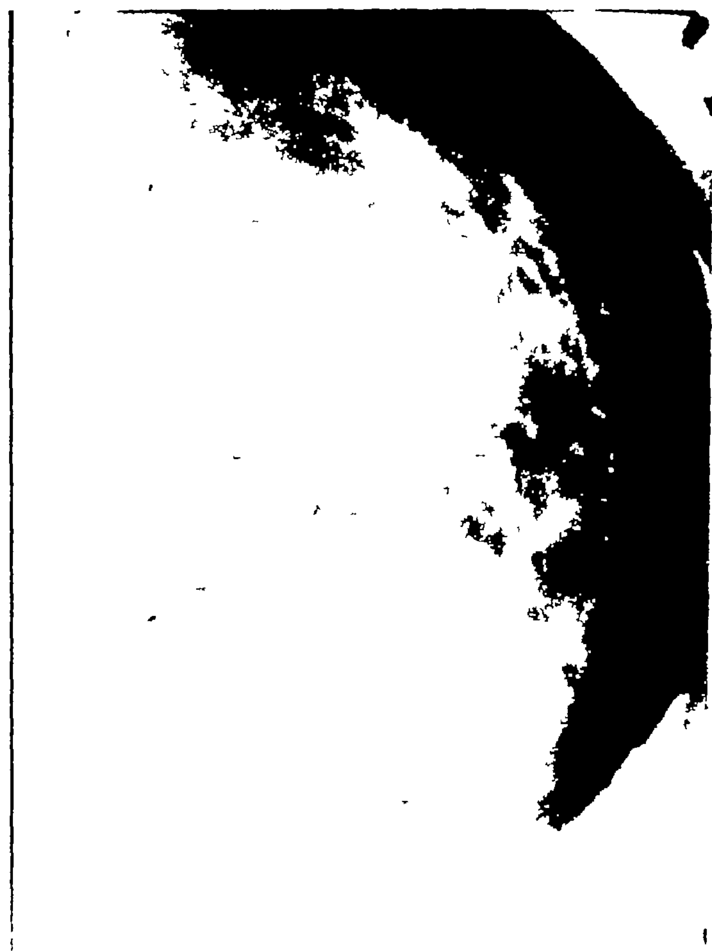
The x-ray film shows dilated, partly beaded ducts running to the nipple They emerge from an irregularly quadrilateral area of "ground glass" density in which the breast pattern is no longer clear (arrow). Operation showed a lesion consisting of soft discolored tissue surrounding ducts filled with grumous material—characteristic of plasma cell mastitis The roentgenographic diagnosis was a difficult one and could not have been made apart from the history and the presence of secretory disease in the contralateral breast.

A′. Drawing of x-ray film.



FIG 140 A

normal breast, followed a short time after by pain and later by a tender mass (fig. 143). The skin may be reddened, occasionally discolored. The sequence indicates rupture of an inflamed duct wall with extravasation of blood and discharge of the contents into the surrounding tissue. A reaction is set up akin to fat necrosis Traumatic fat necrosis, also a form of chemical mastitis, is excluded if the trauma is only slight, pathologic examination shows secretion in the ducts in plasma cell mastitis, but none in traumatic necrosis In both the pain and redness subsides in a few days and the mass becomes smaller This symptom complex is



A

Fig. 141. C 1086 Secretory disease with extensive calcification of ducts. Age sixty years Pain left breast three months ago Breast became red. Two weeks later there was abundant discharge of thick yellow material from the left nipple After this the pain subsided and was only felt occasionally. Discharge from the right nipple was also present, but the breast was painless. On examination the breasts were large and pendulous Both nipples were retracted and a small amount of thick discharge could be expressed from each. Thickened ducts were palpable Some were very hard. There was a thickened area beneath the left nipple Smears from both nipples showed secretory disease No operation

X-ray films of left (A) and right (B) breast showed very extensive calcification along the line of ducts. Both nipples were retracted



FIG 141 B

somewhat rare (7 per cent of all cases), but when it does occur it is pathognomonic.

While most patients with plasma cell mastitis exhibit pain as a prominent symptom, a few, especially among the older women, deny having pain or tenderness There is no correlation between pain and nipple discharge. A nontender lump naturally leads to suspicion of cancer In these patients the x-ray film is the most satisfactory means of clinching the diagnosis

Roentgenologic examination has afforded considerable assistance in the diagnosis and identification of secretory disease and has made a notable contribution to the elucidation of its natural



FIG. 142 Calcified masses in the breast of an old woman.

history. The x-ray appearances, although highly characteristic, vary with the age of the patient and the length of time the disease has been present. In young women with a milky discharge the affected areas are hazy. The texture is similar to that seen in lactation and without a history might occasionally be mistaken for the puerperal state The film is apt to show dilated ducts beneath the nipple resembling those of pregnancy The ducts of older women are often irregularly dilated and have a beaded appearance, easily confused with papilloma. Longstanding fibrosis around the lacti-

ferous ducts is discerned as an opacity shaped like a truncated cone with its apex at the nipple. When plasma cell mastitis is also present, ill-defined flame-shaped shadows spread from the fibrous area toward the base of the breast. This pattern, although only present in certain advanced cases, is highly characteristic (figs 139, 143)

In general, plasma cell mastitis betrays itself by indistinct smudgy opacities which may be unilateral or bilateral (fig 140) They vary greatly in extent and numbers The diagnosis is helped by seeing accompanying signs of secretory disease on the x-ray film. In the absence of such signs the differentiation from other lesions may be impossible

A few small calcified particles in the region of ducts affected by secretory disease of some duration are a fairly common finding on correctly exposed films More spectacular is extensive calcification of ducts occasionally seen in longstanding cases in elderly women (fig 141) Rarely, there may also be irregular calcified patches similar to those sometimes present in healed fat necrosis (fig 142) These probably indicate an old focus of plasma cell mastitis which is pathologically a similar lesion. It is obvious that however startling the roentgenologic appearance in these cases, the lesion is quiescent and surgical intervention is not required.

Pathology The most obvious feature in a breast with secretory disease is the extrusion of wormlike casts from the ducts Beneath the nipple the ducts are usually thick-walled and dilated (figs 143, 144) In longstanding cases they may be matted together in one unyielding fibrous mass Dilatation may be uniform or varicose. In very advanced cases distended ducts may be seen throughout the breast (fig 146) Cysts are not rare although they are seldom as large as in mazoplasia cystica. The more recent the case and the farther the ducts from the nipple the less the fibrosis When the dilated ducts are followed by means of serial sections through the entire breast they are found to end in a cluster of small cysts generally situated at the periphery of the breast. These represent the remains of a lobule and were probably the site of the original lesion.

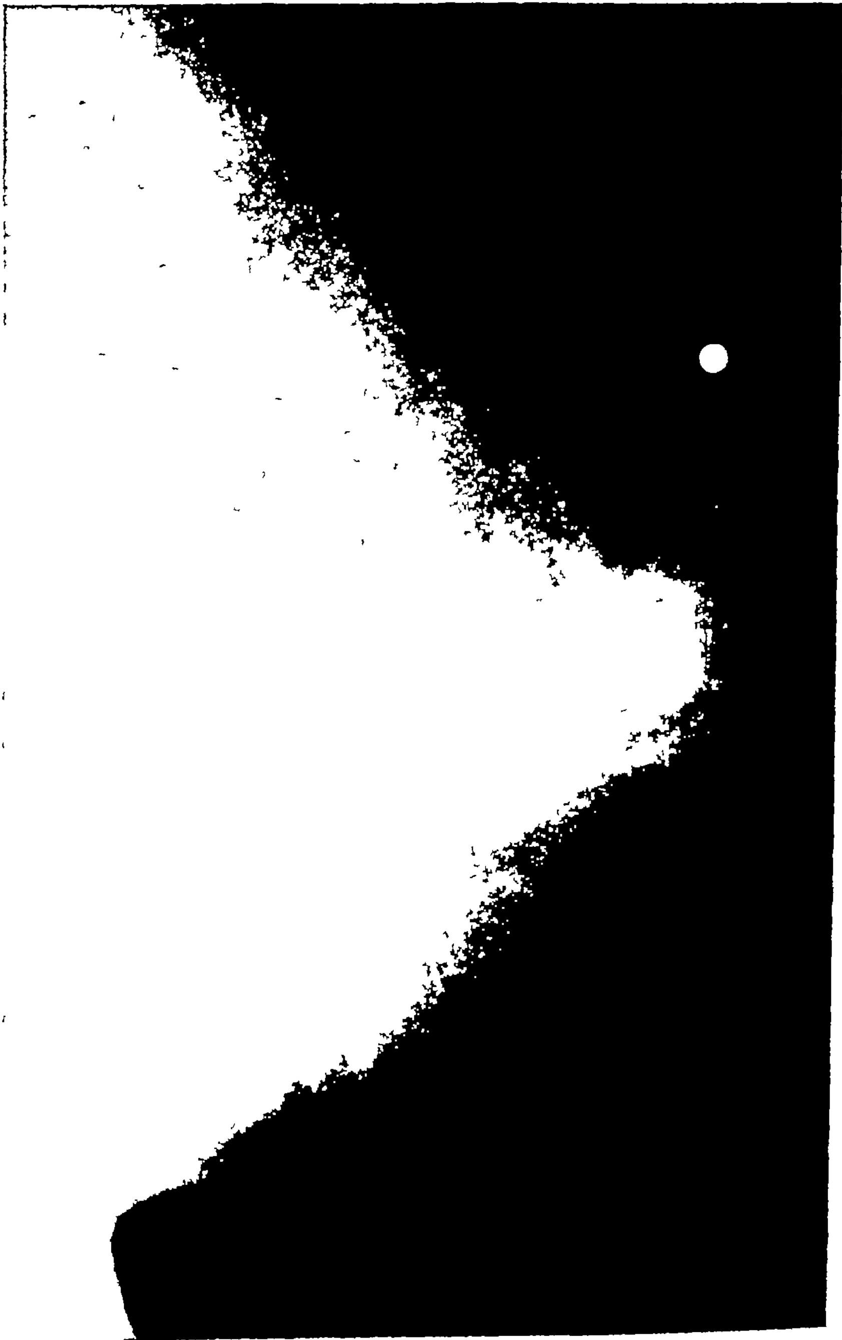
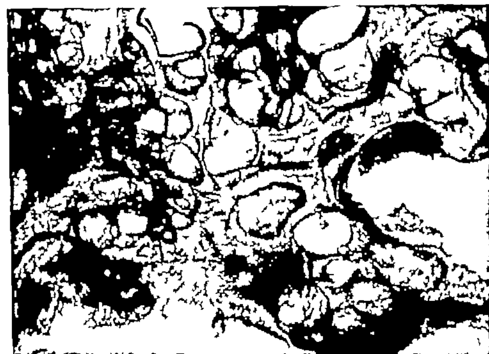


FIG 143. A

Microscopically, secretion in the ducts may be amorphous with occasional shadows of colostrum cells (fig 149), or the ducts are packed with colostrum and inflammatory cells, together with fatty acid crystals The state of the lining epithelium varies The early



B

FIG 143 C 250 Secretory disease. Plasma cell mastitis Age fifty years Two weeks before examination patient bumped her left breast. Four hours later she felt pain. On examination there was redness of the skin and an indefinite mass beneath the nipple area.

A. X-ray film presents an opacity beneath the nipple with flamelike projections extending toward the base of the breast. Microscopically this was an area of plasma cell mastitis

B Slicer section of ducts immediately beneath the nipple. The ducts are cut transversely Secretion is seen in many of them in others it has fallen out in processing The walls of the ducts are moderately thickened.

The findings indicate that the patient had asymptomatic secretory disease, probably for years, and that trauma initiated a sudden flare-up of plasma cell mastitis.

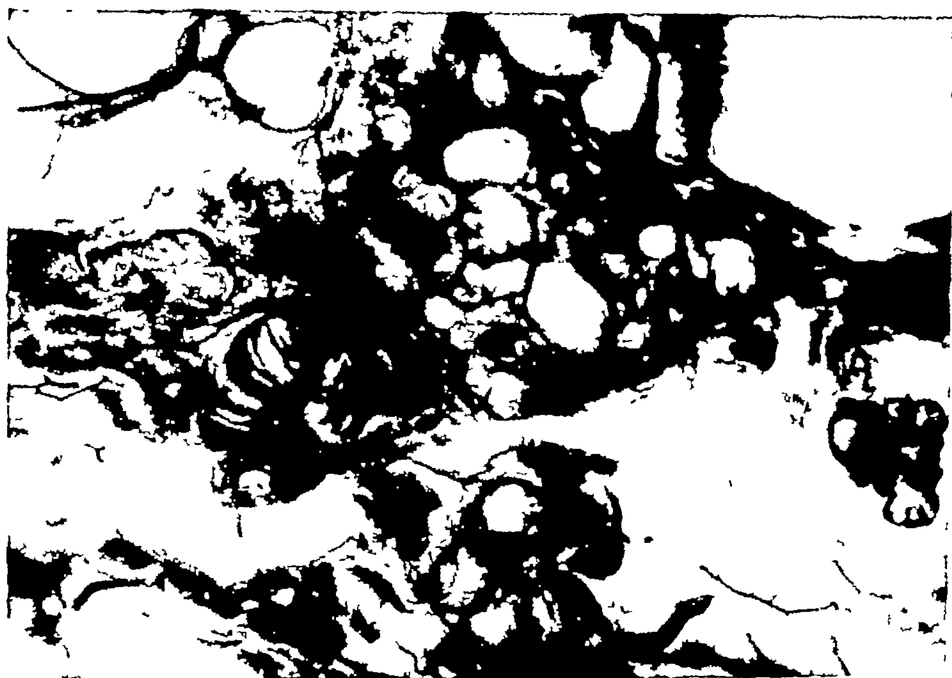


FIG 144 C 37. Secretory disease Early fibrous thickening of wall of lactiferous ducts Age thirty-seven years Slicer section shows dilated ducts in subareolar region. Secretion has dropped out of some of the ducts in processing

phase is one of hyperplasia with differentiation of many of the cells to the secretory type. It is not uncommon to find ducts lined by heaped-up cells with clear vacuolated cytoplasm having their origin in the epithelium or in fat-laden histiocytes* which have migrated there (fig. 146B) The hyperplasia is sometimes sufficient to produce small polyps, but these generally disintegrate. The myoepithelium is also hyperplastic The late stage is marked by degeneration of the secreting epithelium When this happens on a large scale the duct is lined by a flattened membrane The myoid forms part of the general fibrosis in and around the ducts Secretion may also be found in ducts lined only by the usual columnar cells. This would indicate that the secretion originated farther back

*"Histiocyte" is used in deference to most pathologists, actually much of the evidence suggests a myoepithelial origin

in the mammary tree. Examination of the adjacent lobules often reveals ductules filled with secretion and lined by secretory cells

The above description corresponds to the average uncomplicated case of secretory disease. The nature of the earliest lesions may be deduced from studies of the breasts of younger women of child-bearing age who were operated on for a tender mass in the acute or recent stages of the disease. In them it is obvious that the lobules are more affected than the ducts Grossly the tissue is soft Microscopically, lobules are seen which mimic those of the pregnant or possibly lactating breast (fig 147) This is evident in uninflamed areas The secretory changes are present in the epithelium of the prelobular ducts as well as in the acini The myoepithelium is hyperplastic both in lobules and in ducts In lobules the myoepithelial cells may be hypertrophied as in pregnancy As in other dysplasias the secretory areas are local rather than general and are variable in their extent.



FIG 145 C 82. Fibrosis of ducts in long standing secretory disease. Age fifty years

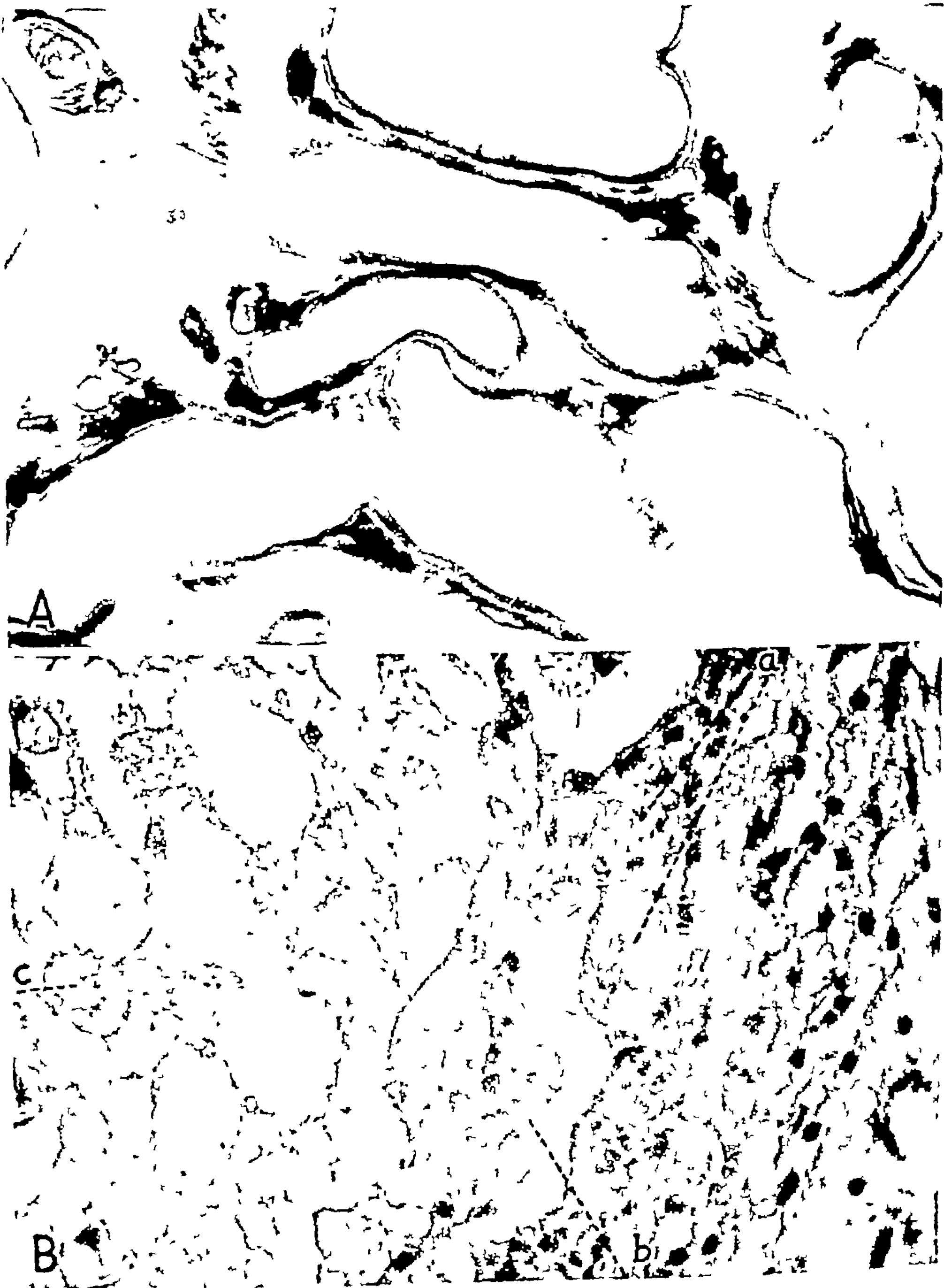


FIG 146.

Apart from a few cases in older patients with nipple retraction or nipple discharge, most women come to operation on account of plasma cell mastitis In past decades only the generalized type of plasma cell mastitis was recognized and it was thought of as a rare disease. Actually minor forms are common and the lesions range from microscopic foci to confluent areas involving the greater part of the breast (fig 152) In one case all but the posterior rim of the gland was involved. Both breasts may be affected Grossly the affected tissue is soft, sometimes pale with yellowish points, sometimes discolored in varying hues of red, brown, or greenish yellow The presence of grumous material in the adjacent ducts clinches the diagnosis

The histological picture of plasma cell mastitis is as variable as the extent of the disease. In the focal type when the areas involved are small, not all variations can be expected to be present in any one case. The principal lesions to be looked for are (a) ulcerations in the duct wall, (b) necrosis of one or more ducts and of the surrounding fat, (c) inflammatory exudate, (d) fibrosis, and finally (e) calcification. Small ulcers starting in the intima are due to irritation by degenerated secretion. They are sources of blood and inflammatory cells in the nipple discharge. Ulceration leads to necrosis which is often so severe that the duct wall is destroyed and the original structure is replaced by a ring of necrotic material surrounded by a broad zone of inflammatory cells The inflammatory exudate may break through the wall of an

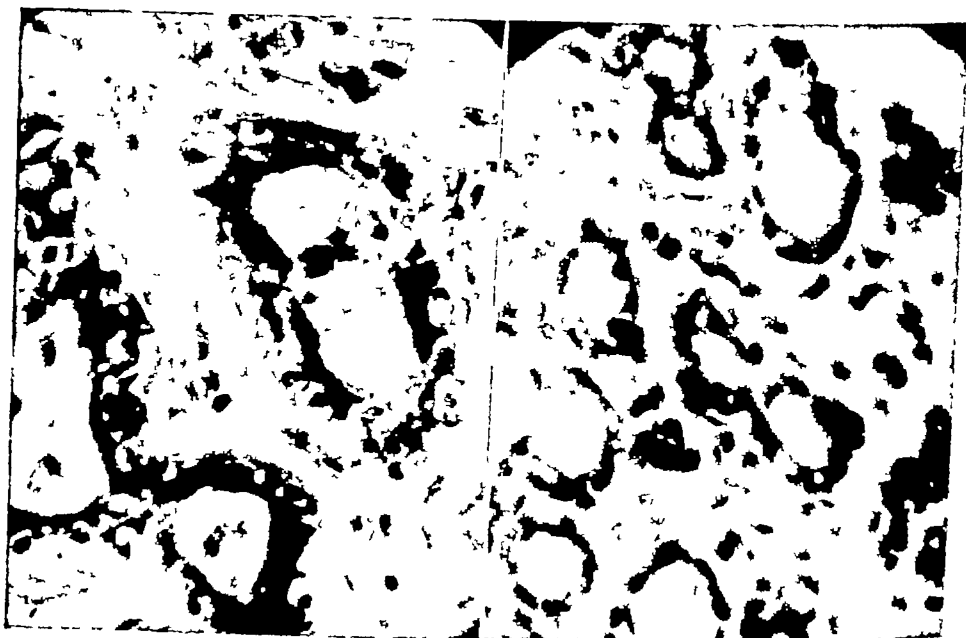
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FIG 146 Generalized secretory disease.

A. Age forty nine years Patient had ten children. Her menstrual periods had been regular At operation the breasts consisted of enormously dilated ducts filled with inspissated secretion. The lobules were atrophic. One patch of plasma cell mastitis was present.

B Age thirty-eight years Photomicrograph of part of the wall of a dilated duct. At (a) are colostrum corpuscles in the epithelium lining the wall of the duct. At (b) colostrum cells in a cavity formed by degeneration of epithelial cells in the center of an area of hyperplasia. At (c) colostrum cells in the lumen of a duct. (Hematoxylin and eosin, high power, 4 mm. objective.)

FIG 147 A



B C

adjacent duct with invasion of its lumen by inflammatory granulation tissue (fig 139) The inflamed tissue may protrude into the duct as a polyplike mass covered by degenerated heaped up vacuolated secretory cells in process of degeneration and desquamation (fig. 157) The inflammatory cells may be of every type. Plasma cells are common, but often lymphocytes predominate. Polymorphs may be present in large numbers as are fat-containing "histiocytes" Giant cells and fatty acid crystals are often but not always present (fig 148) Rosettes are usually found only in advanced cases Fibrosis is a prominent feature if the mastitis has been present for some time (fig 145) The late stages of secretory disease may be marked by extensive and bizarre calcification. This is usually confined to the ducts, but where there has been fat necrosis as in plasma cell mastitis, very unusual forms of calcification are sometimes found (fig 142) Although easily picked up on the x ray film, this development has been neglected by the pathologist. The process appears to be similar to that seen in fat necrosis in other parts of the body

Smears from the nipple discharge, when present, are usually pathognomonic (fig 149) Unless degeneration of the duct con-

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FIG 147 C 100 Secretory disease in a woman of childbearing age —comparison with early lactation involution. Age thirty five years The patient bumped her right breast against a door six days before examination The injury was slight. She first noted a painless mass soon after injury, but two days later the mass became painful and the skin over it was reddened. There was a slight discharge from the nipple. On examination, a tender mass 4 cm. in diameter was found in the nipple area. The pathologic specimen showed a severely inflamed area with brownish, wormlike casts exuding from dilated ducts

A. Frozen section stained with hematoxin and Scharlach R shows part of a lobule and a small duct. The lumens of some of the acini are filled with fatty secretion as is that of the duct. The surrounding tissue is heavily infiltrated with inflammatory cells

B Part of a lobule. The lining cells of the acini are mostly of the secretory type.

C. Breast four days postpartum, early lactation involution. The acinar epithelium resembles that of B.

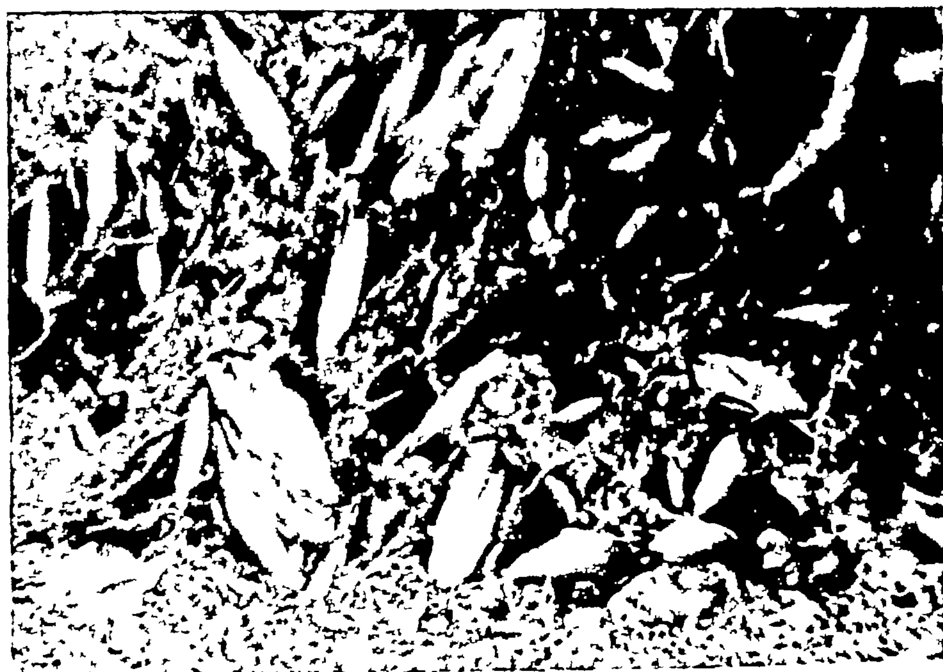


FIG 148 C 181 Focus of plasma cell mastitis. Age fifty-one years Paraffin section showing giant cells and clefts originally filled with fatty acid crystals.

tents is far advanced, microscopic examination reveals numbers of colostrum cells. Some may be of enormous size. In many cases the cytoplasm is crammed with fatty particles. The colostrum cells may be derived from epithelium, or, as the older pathologists believed, from wandering cells (histiocytes). The cells are in various stages of degeneration Often the cell itself has disappeared leaving a collection of fat droplets in its place. In most cases, although not in all, fat droplets are scattered through the secretion. In plasma cell mastitis inflammatory cells are also present and may be very numerous Fatty acid crystals may be found and even giant cells and "rosettes," although these last are not common in the smear.

Differential Diagnosis. Secretory disease needs to be differentiated from carcinoma, papilloma, intraductal hyperplasia, from other forms of mammary dysplasia, traumatic fat necrosis and abscess. Onset with pain, a tender mass and discharge from the

nipple indicates plasma cell mastitis Examination of the discharge may confirm the diagnosis The mass in acute cases generally becomes smaller But often the signs are not so clear cut. The greatest difficulty arises when an elderly woman discovers a hard painless lump indistinguishable from carcinoma on palpation (fig 150) There may be no nipple discharge, or to make matters more confusing the patient may give a history of bright blood in a discharge which had ceased before advice was sought. Roentgenographic examination is then mandatory Surprisingly, in some of these cases no tumor is seen on the film. On the other hand, if an opacity is present it will tend to be larger than the mass measured clinically A carcinoma would be smaller and more dense The



FIG 149 Secretory disease, discharge from both nipples

A. Smear from right nipple swollen colostrum cells containing numerous lipoid granules.

B Smear from left nipple amorphous fatty material in which shadows of degenerated colostrum cells can be occasionally recognized.

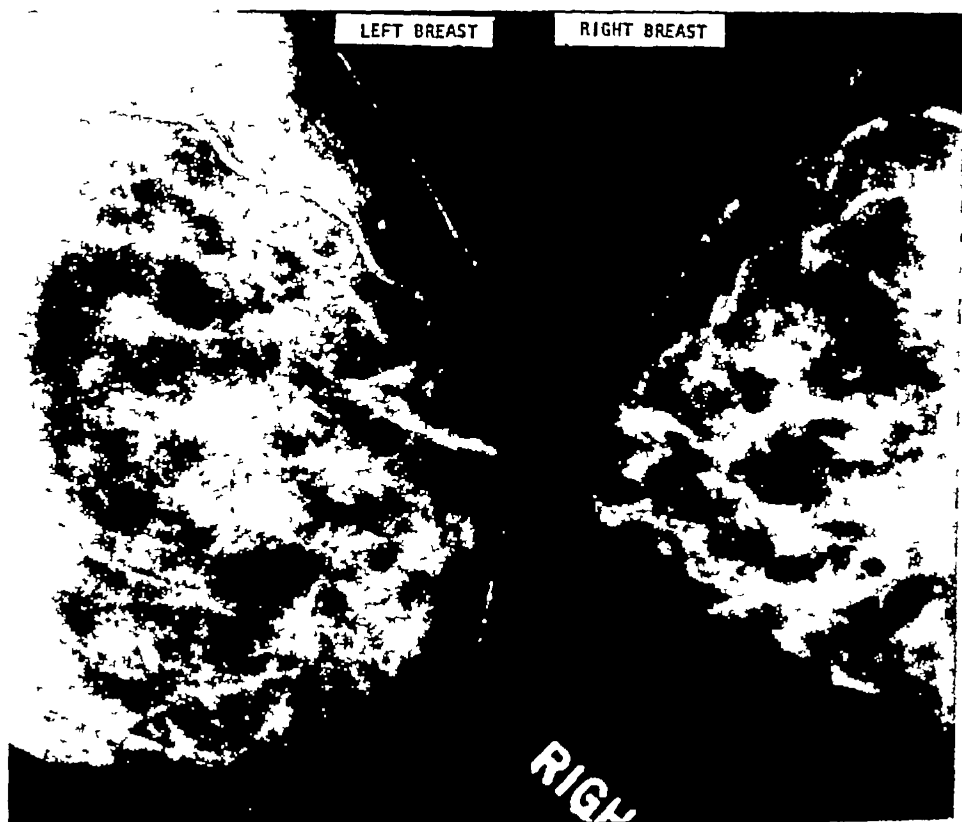


FIG 150, C 711 Plasma cell mastitis simulating carcinoma Age sixty-five years. The patient was admitted to hospital with a diagnosis of carcinoma of the right breast Two weeks before, she had pain in the right breast for one day and discovered a mass Examination one week later revealed a red indurated area around the nipple, overlying a large, hard tumor. The day before operation the redness had disappeared and all that could be felt was a mass 1 5 cm in diameter below the areola Operation showed dilated ducts filled with inspissated black or yellowish material, surrounded by necrotic fat.

X-ray films of both breasts Normal involutional fibrosis is partly overlaid by indistinct fluffy opacities Both breasts show a calcified artery in the upper part. The veins are dilated Dilated ducts are seen on both sides, but are more obvious on the right Rather coarse calcified particles having a linear arrangement are seen along a duct beneath the right nipple Farther back there is a cystlike expansion of a duct (arrow) A few coarse calcifications are seen in the left breast The over-all picture is that of secretory disease

No tumor mass corresponding to that felt clinically is present on the film and since the film is technically excellent, carcinoma is thereby ruled out

margins would be more sharply defined than in plasma cell mastitis The tentacles in carcinoma usually cut across the line of the trabeculae. The extensions of plasma cell mastitis spread along the trabeculae. Examination of the other breast would show secretory disease.

Clinically, papillomas are confused with secretory disease on account of discharge which may occur in both. As in secretory disease a mass may or may not be present. Pain is unusual in papilloma except when a cyst is suddenly distended by hemorrhage. In papilloma, the discharge is serous or frankly bloody, and the diagnosis is established by finding pieces of the tumor in the smear *For this more than one examination is often necessary* The x ray film is of less value. Varicose ducts are characteristic of multiple intraductal papillomas, but may appear in secretory disease. A truncated cone appearance beneath the nipple and flame-shaped opacities are seen in secretory disease, but not in papilloma. However, the coexistence of the two conditions cannot be ruled out.

Intraductal hyperplasia of the precancerous type is extremely hard to recognize without the help of the x ray film. A few cases have nipple discharge which is apt to be clear rather than bloody The smear may suggest carcinoma, but palpation would reveal at most only dilated ducts The x-ray film usually shows irregularly dilated ducts and sometimes fine calcifications The size of the particles varies, but in most cases they are minute. Similar calcifications are found here and there in the fibrous walls of the ducts in secretory disease, but their density may be compared to that of an eggshell. They are nearly always elongated and show polarity in that their long axes lie in the line of the ducts The fact that they are most often situated in the wall of the duct and not in the lumen as in hyperplasia gives them a characteristic contour well seen in advanced lesions A transverse view of a calcified duct shows a sharply defined dead-white ring with a clear central lumen Taken longitudinally the duct appears as a cylinder with open ends (fig. 141) The lesions in both breasts are usually

similar, intraductal hyperplasia may be bilateral, but this is not t rule.

Secretory disease is differentiated from mazoplasia cystica the location of the lesions which are mainly in the subareolar ar whereas those of mazoplasia are apt to be central or in the upp outer quadrants. Cysts in secretory disease are few, in contrast the numbers often seen in mazoplasia. Isolated secretory cysts a sometimes found in mazoplasia cystica, and would generally see of small importance. Their preoperative diagnosis is scarce possible. Solitary inflamed cysts may be of secretory origin, but most of them the characteristic epithelium is destroyed and th exudate is not typical of plasma cell mastitis. As has been sai secretory disease may be combined with other forms of dysplasi It is seldom more than a minor feature and would be includ under the term of mastopathy. Plasma cell mastitis is rarely se in mixed dysplasia, perhaps because of the limiting effect of th fibrous tissue which is an important component of mastopathy.

Traumatic fat necrosis produces a cell reaction similar to that plasma cell mastitis This is to be expected since fat necrosis is feature of both. But fat necrosis due to trauma is so sudden that th cellular exudate is often confined to the periphery and has no reached the center of the structureless necrotic mass Furthermor extensive hemorrhage may be expected, in contradistinction to th occasional small effusions seen in plasma cell mastitis.

Abscess may be closely simulated by the acute form of plasm cell mastitis, but the experienced radiologist can usually distinguis between them. The diagnosis of abscess is facilitated by the fac that it occurs mostly during the puerperium, and is almost neve bilateral. Nonpuerperal abscess, on the other hand, is frequentl based on secretory disease Mammillary fistula, the form o abscess most easily confused with secretory disease, is discusse under abscess

According to Mavis Gunther a comparable sequence to th seen in secretory disease and plasma cell mastitis occurs in puer peral mastitis. She believes that rupture of a duct in a turgescen

breast with discharge of milk into the tissue is responsible for puerperal mastitis Some cases recover spontaneously or with suitable treatment, others become infected and go on to abscess

Secretory disease is a definite entity, easily recognizable roentgenographically and pathologically, and often clinically It is a rather mild disorder The chief complication is plasma cell mastitis, but abscess occasionally supervenes Because of the rather bizarre manifestations patients are operated on much more frequently than they deserve. Removal of lactiferous ducts in secretory disease is needless and may be mischievous If an operation is deemed necessary it would be preferable to remove the diseased area, i.e., the lobe of which the duct is the outlet. In most cases it is probable that the lobules in the isolated area undergo atrophy and perhaps fibrosis and are then harmless, but little has been gained by sectioning the duct. Should infection be present the diagnosis would be changed to mammillary fistula and be dealt with in the manner advocated by Atkins The worst aspect of unnecessary surgery is that carcinoma does occasionally occur in a breast which is also the seat of secretory disease but never, as far as our experience goes, at the same site (fig 151) Neither Foote and Stewart (1942) nor Tice (1948) could trace any direct connection between malignant areas and "comedo mastitis" This means that unless the carcinoma is sufficiently advanced to call attention to itself the surgeon will be satisfied with removal of a few diseased ducts and the real offender will be left in situ. Our figures are not large enough to show whether there is a positive correlation between secretory disease and carcinoma Until more evidence is available the best means of diagnosis is the x-ray film. This is not infallible, but in nearly all cases of carcinoma it will reveal either the growth itself or a suspicious area which should be investigated by the surgeon.

Secretory disease, like other mammary dysplasias, is due to hormone imbalance and it is reasonable to suppose that the hormones connected with lactation are at fault. Irregular or imbalanced stimulation by these hormones could well account



FIG 151. A



B

for the phenomena observed and would explain the difference between secretory disease and other dysplasias which stem from excess of estrogenic hormones We are inclined to believe with Dawson that artificial drying up of milk predisposes to galactocele, which is a variant of secretory disease. The question whether the disorder is more likely to occur in mothers who nurse their children than in those who could and do not nurse deserves further study

MASTOPATHY (SCHIMMELBUSCH S DISEASE)

The term mastopathy is reserved for advanced cases with multiple dysplasias It may be regarded as the end result of recrudescence and healing of a variety of lesions Each deviation from the normal must be sufficiently developed to merit diagnosis in its own right When the breast shows predominance of one type with only minor variations, the pathologic designation is assigned to the predominant lesion. Since different areas in the breast are occupied by different kinds of dysplasia a paraffin section is usually insufficient for complete diagnosis The entire breast needs to be studied. Clinical examination is not very satisfactory Serial sections of the whole tissue can only be made after operation, but what is required is an inspection of all suspicious areas before surgery is undertaken In contrast, the radiologist is able to see everything mirrored on the x-ray film He can get a good over-all picture of what is going on in the breast and is therefore in a position to indicate the best location for biopsy (fig 105)

Mazoplasia cystica is practically always present together with dilated ducts filled with secretion and occasional secretory cysts

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FIG 151 C 378 Secretory disease and carcinoma in the same breast. Age forty-seven years The patient complained of a mass in the left axilla noted ten days. The secretory disease was asymptomatic.

A. Slicer section shows numbers of dilated ducts filled with thick secretion.

B Carcinoma deep in the breast and extending to the axilla There was no connection between the carcinoma and the area of secretory disease.

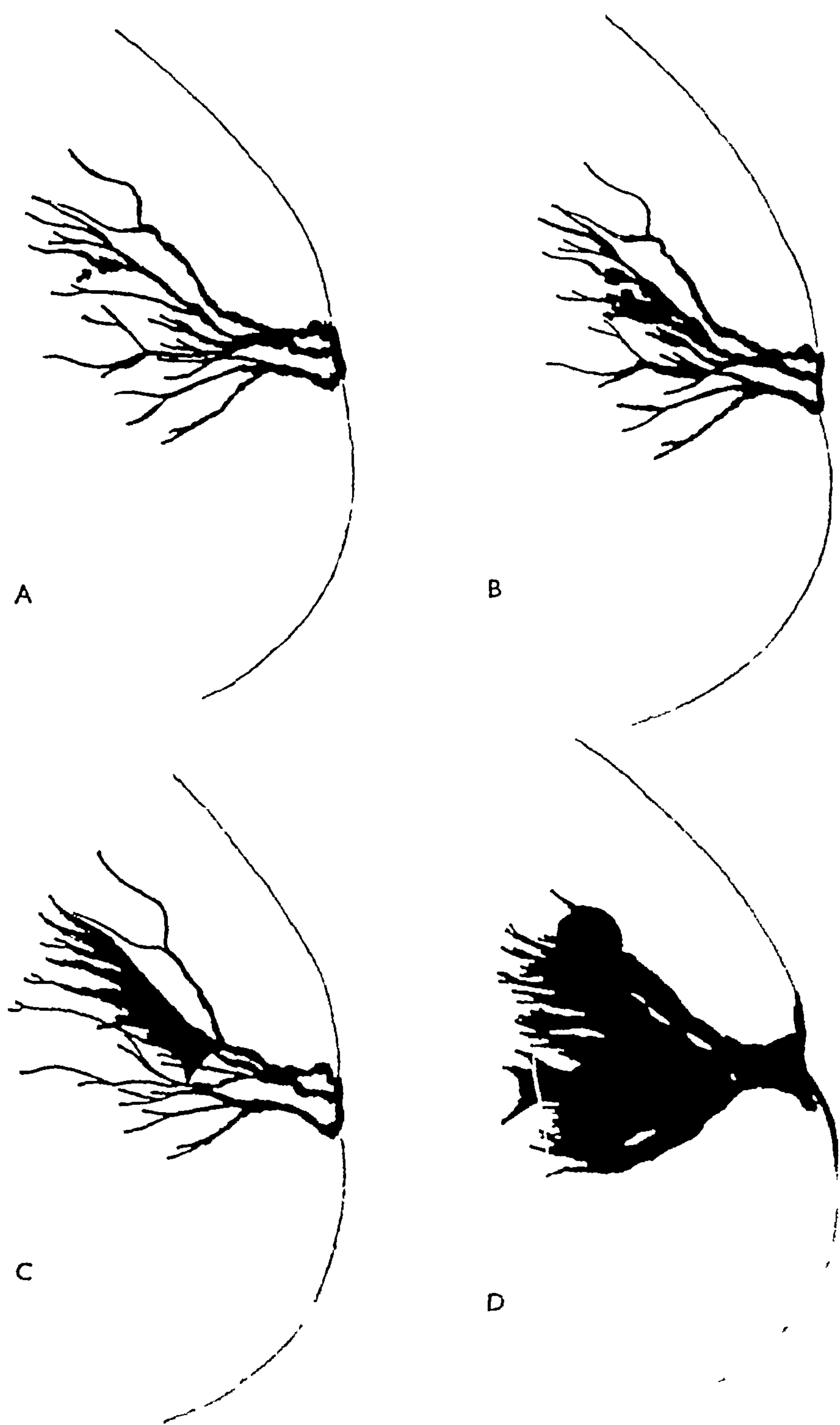


Fig 152

Fibroadenomas are common. Fibrosis, due to healing of various lesions, is nearly always a conspicuous feature. It may be of any type, but is usually nonspecific. Over and above the dysplasias proper, small foci of intraductal hyperplasia and small papillomas of the benign type are not uncommon

Roentgenographically, these breasts present features associated with adenosis, mazoplasia fibrosa and cystica, fibroadenoma, secretory disease, cysts of various origins, and fibrosis consequent on healing of some of the lesions (fig. 153) Pathologically a minor degree of intraductal hyperplasia and papillomatosis may be met with, but generally speaking the foci are too small to be discerned on the x-ray film The above changes are scattered irregularly through different portions of the breast and may produce a bizarre effect. Since none of the lesions is predominant and it is not always possible to diagnose each one separately, the general appellation of mastopathy, which is actually only a diagnostic compromise, has been given to this group Each of the component lesions in mastopathic breasts has been described separately under its own heading and nothing more remains than to realize that in these cases the

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FIG 152. Varying degrees of plasma cell mastitis (Diagrammatic reconstructions from a series of x ray films)

A. The lactiferous ducts are dilated and beaded due to secretory disease. The disease extends into the ducts of the second and third order In one of these a small irregular area of plasma cell mastitis (arrow) extends beyond the confines of a duct.

B Shows several patches of plasma cell mastitis involving one lactiferous duct and its branches

C. Plasma cell mastitis is not confluent, but is still confined to one duct system. One edge is straight, and sharply defined. This may be caused by a duct which has resisted the disintegrating process

D Generalized plasma cell mastitis. Only the posterior portion of the breast is unaffected. The lesion has a flamelike contour Here and there margins are sharp, some are rounded and resemble cysts At this stage the chemical mastitis may mimic abscess.

The nipple is moderately retracted. In secretory disease gradual retraction is usually due to fibrosis, but in acute inflammation the nipple may appear pulled in due to swelling of surrounding structures.



Fig 153.

roentgenologist simply sees two or more of these lesions irregularly distributed through the breast. In the older patient, fibrosis due to healing of some lesions is nearly always a conspicuous feature It may be of any type but is usually nonspecific. If there is much fat in the breast, the fibrosis is easily discerned, but if the breast is fat-free and compact, the amount of fibrosis cannot be visualized The multiplicity of lesions and the amount of fibrosis may interfere with diagnosis of a small cancer, impossible to distinguish clinically from other lumps in the breast (fig. 176)

Because of the numbers and differences in type of lesions in mastopathic breasts, these patients are unfortunate in that they often undergo multiple operations without cure and even without improvement in their symptoms The saving feature is that women with advanced mastopathy seldom develop cancer, in our experience only about 7 per cent of carcinomas occur in mastopathic breasts

MAMMARY ABSCESS

Breast abscess is a fairly common, although generally unnecessary, complication of the puerperium, but it is also seen apart from the gestation cycle and even occasionally beyond the menopause.

The older classifications of mammary abscess are open to objection on various grounds The division into puerperal and nonpuerperal, for example, does not take into account recurrent abscess which may begin in one phase and be reactivated in another

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FIG 153 C 2789 Mastopathy Age fifty-six years Admitted for carcinoma of the right breast.

X ray of the left breast shows several irregular opacities with indistinct margins. There is general disturbance of the architecture, characteristic of mastopathy The largest opacity in the upper outer quadrant (marker) might be confused with carcinoma, but the processes run in the line of the trabeculae.

Operation in the area of the dominant mass revealed several small to medium cysts together with adenosis, intraductal hyperplasia and papilloma

B



A

Fig. 154

phase of the gland's history Acute, chronic, and recurrent are good general yardsticks, but they permit of no exact demarcation of individual lesions Classification according to the position of the abscess within the breast has certain etiologic value, but is not always exact because abscesses have a habit of spreading from one part of the organ to another and the site of origin may be difficult to trace. The most satisfactory classification is that of superficial and intramammary formulated by Gunther (1956) for pregnancy and lactation, but equally relevant in nonpuerperal cases Division is based on etiology and is clear cut. It is practical in that it facilitates interpretation of x-ray films and has important implications with regard to treatment. Secondary abscesses due to septicemia or to infection from adjacent structures are not dealt with here. Retromammary abscess may be an extension from an intramammary infection, but usually has its origin outside the breast.

Superficial abscesses are due to cracked nipple, infected Montgomery gland, or skin infection (fig 154) The cause is usually self-evident. They seldom affect the gland itself and there is no need to elaborate on their pathology and roentgenography

Experience has shown that the evolution of a breast abscess is more easily followed on the x-ray film than clinically The extent and distribution of the inflammatory reaction is visualized and serial examinations will show whether the lesion is becoming encapsulated or whether cellulitis is spreading through the breast. An acute abscess appears on the film as an irregular density often with flame-shaped extensions At first and in rapidly spreading

FIG 154. Acute superficial abscess

A. Age twenty two years. Tender mass in right nipple area, following injury two weeks before. The abscess was pointing through the skin. Roentgenogram shows an irregular opacity [illegible] to thick skin.

B Age twenty three years. The patient noticed a "pimple" on the areola ten days before. When seen, she presented a nodule 2.5 cm. in diameter surrounded by reddened area 2.5 cm. in diameter. The roentgenogram shows a more or less circumscribed opacity under the skin of the areola. The skin is thickened. The abscess probably originated from an infected Montgomery gland.



B



A

Fig 155

lesions the boundary is indistinct Localization of the abscess is shown by the development of sharp margins resembling those of a cyst (fig 155A) The center becomes structureless Encapsulation is apt to be incomplete for some time. Often broad tentacles are seen emerging from the abscess margin (fig 155B)

An important sign which often helps in differential diagnosis is edema of the skin. Thickened skin is seen on the film in all active superficial lesions and in deep abscesses, if they are large Unfortunately, cutaneous edema may be absent in a small deep-seated abscess which is most difficult to diagnose. Distended veins are a feature of the acute stage, they persist as long as the infection is active.

The chronic stage of an abscess, especially in nonpuerperal cases, is difficult to distinguish from a cyst, both clinically and by x-ray (fig 155) The outlines of the abscess are sharp In the absence of history an obsolescent lesion would probably be mistaken for a cyst, but if inflammation is still present in the surrounding tissue, portions of the circumference will appear slightly blurred An old abscess may be a smooth round structure, but if

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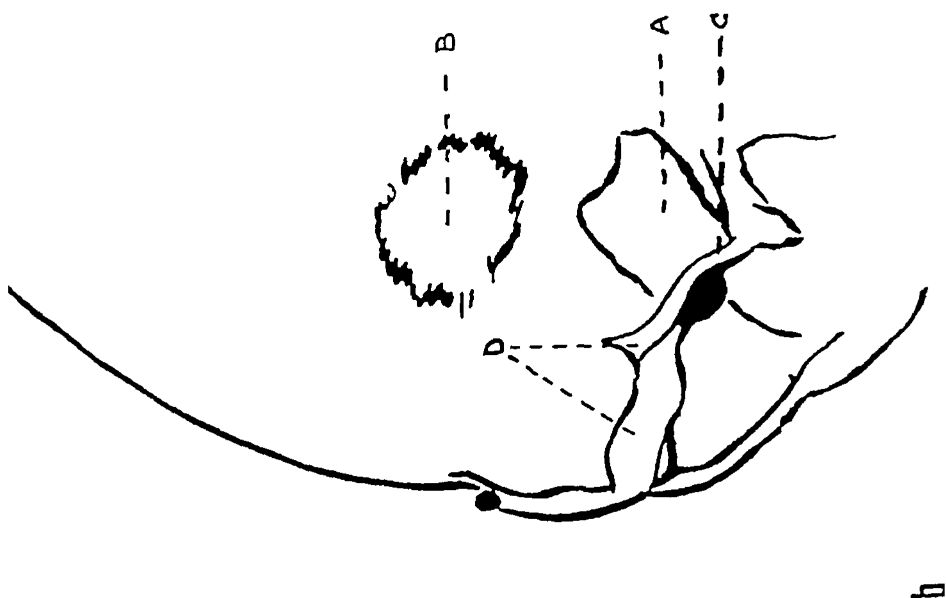
FIG 155 Chronic intramammary abscess

A. Age twenty four years. Painless mass above right nipple noted five months. When seen it was 8 5 cm. in diameter Both nipples were retracted but the right was also edematous Youngest child, three years old, was nursed for ten months from this breast. The condition of the left nipple made nursing impossible.

X ray film shows a cystlike mass The margin is sharply defined posteriorly, but obscured elsewhere by swollen trabeculae. The vessels are distended. The density of the mass is not uniform and this was reflected in the pathologic specimen which consisted of a large, loculated, chronic abscess, with small abscesses nearby

B Age thirty-eight years Thick whitish discharge from left nipple for one year A mass appeared in the subareolar area six months before and increased steadily with occasional exacerbations of pain.

Roentgenogram shows a very large loculated mass with a smooth edge except posteriorly where the margin is irregular Large tentacles issue from the mass, especially at the lower edge. The tentacles are fewer than in carcinoma and are broad and rather straight. The nipple is not shown but was retracted and edematous



b

extensions and daughter abscesses have formed at any time, differences in density may be discerned within the lesion (fig 155) The pattern so formed differs from anything found in cysts Edema of the areola and surrounding skin is a feature of all forms of subareolar abscess The nipple may be actually retracted, but more often appears so because the swelling pushes up the adjacent tissues while the nipple itself is anchored by the lactiferous ducts A large encapsulated abscess pushes the mammary tissue to one side, a large cyst may do so, but has less effect because it is itself a part of the mammary tissue, whereas an abscess acts as a foreign body

Healing may take place in a breast abscess, as elsewhere in the body, by fibrous replacement. The pus is slowly absorbed. The abscess cavity is replaced by granulation then by fibrous tissue At this stage x-ray diagnosis is extremely difficult In fact, the patternless fibrous tissue forming part of the healing abscess is usually impossible to distinguish from nonspecific fibrosis such as might be due to inflammation of the surrounding tissue Diagnosis could scarcely be expected unless the process had been followed to its conclusion by means of serial films In a larger abscess grumous or inspissated material may remain indefinitely Occasionally calcification supervenes

Recurrent Abscess and Mammillary Fistula Recurrent abscess may be the result of inadequate treatment. But there is one form, first described by Zuska, Crile and Ayres (1951) and named mammillary fistula by Atkins (1955), in which recurrence is almost inevitable unless the condition is rightly understood and proper surgical measures are taken (fig 156) In general the history is that of an abscess in the subareolar area which was incised but

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FIG 156 C 751 Mammillary fistula. The roentgenogram (a), shows the nipple partly overlaid by a fold of thickened skin. The main abscess is just beneath the nipple and another abscess is seen nearby The sinus tract was not injected with an opaque medium. (b) Diagrammatic drawing of fig 156 (A) abscess beneath nipple, (B) secondary abscess, (C) nipple (D) edematous folds of skin.

The diagnosis of hematoma is usually dependent on the history In the early stages the x-ray film shows a dense opacity As organization proceeds and the hemoglobin is absorbed, the mass becomes less dense and smaller, the margins are faintly spiculated due to fibrosis Finally only a fibrous scar remains

Occasionally an area of fat necrosis becomes encapsulated and resembles chronic abscess on the x-ray film. Recourse must be had to the history In fat necrosis shrinkage of the area and disappearance of symptoms is much more rapid than in abscess

Secretory disease may not give much trouble in the differential diagnosis until it is complicated by plasma cell mastitis or an inflamed cyst. By itself secretory disease is characterized by the secretion of milklike substances in the absence of pregnancy or lactation and is often asymptomatic. Pain is usually an indication that chemical or plasma cell mastitis has supervened, but may be a sign of inflammation in a secretory cyst. On the x-ray film, the margins of an inflamed cyst tend to be blurred due to perifocal edema and increased vascularity Differential diagnosis from abscess is of academic rather than practical importance, operation is indicated in any case for cure of pain as well as for prevention of abscess

Differentiation of abscess from plasma cell mastitis is important and often difficult. To open and drain an area of chemical mastitis is to invite infection, neglect of an abscess may result in cellulitis On the x ray film an irregular opacity with poorly defined margins and flamelike extensions would suggest plasma cell mastitis, but the lesion is not always clear cut. Edema of the skin is the rule in abscess unless the lesion is deep-seated, in plasma cell mastitis cutaneous edema is not common and is never more than moderate Absence of underlying secretory disease would strongly favor abscess Its presence is less significant. Where doubt exists the differential diagnosis must be made on clinical grounds The initial fever, pain and swelling decrease in chemical mastitis, they increase in abscess

Clinically, adenosis occasionally simulates acute inflammation

and the two are often superficially alike on the x-ray film. Attention to the following points will serve to distinguish them. In adenosis the skin may be reddened, but it is thin and edema does not occur. Adenosis is apt to be bilateral and presents multiple indiscrete opacities Abscess is most often single, although it may present many ramifications; sharp outlines are not present until localization begins, but at this point the distinction between the occasional sharp margins of adenosis and encapsulation of an abscess should be clear. Most abscesses show marked vascular turgescence. It is true that some hyperplasias and notably carcinoma may do the same But enormous veins surrounding a benign lesion require exclusion of abscess before a diagnosis of cyst or adenosis or even plasma cell mastitis is made.

A chronic abscess may be confused with the large cysts of mazoplasia cystica The most important criteria for abscess are tentacles, never seen in cysts, and edema of the overlying skin

Papilloma, in the absence of distinctive nipple discharge, is generally more difficult to distinguish from secretory disease than from abscess Multiple intraductal papillomas are signalized by tortuous varicose ducts and are often bilateral A solitary tumor may occasionally give rise to some difficulty.

Confusion between abscess and carcinoma occurs only rarely, but their occasional resemblance sets a trap for the unwary Abscess is characterized by rapid onset with pain, but this may happen in inflammatory carcinoma. Usually the patient has no idea of the duration of her tumor and only describes the symptoms of sudden onset. On the x-ray film the margins of a carcinoma are irregular and often more sharply outlined, but this is by no means constant. Tentacles are fewer in abscess than in carcinoma, spicules are not an obvious feature. The presence of minute calcified particles emerging from a tumor is proof of malignant growth.

Our roentgenographic studies of mammary abscess and particularly mammillary fistula led us to certain conclusions regarding the etiology of abscess arising within the gland. Gunther has

clearly shown that puerperal abscess is preceded by stasis The pain and swelling accompanying stasis are mistaken for abscess, but pus is not found in the milk for at least two days The best treatment is to empty the breast, and for the first two days the infant may safely be allowed to do this The alternative is a breast pump When treated in the early stages the blocked duct functions again and the condition clears up On the other hand, if milk is not withdrawn from the breast, abscess is liable to develop Until recently we had not thought of secretory disease and chemical mastitis as precursors of abscess, but our studies of cases of mammillary fistula made it clear that a mechanism similar to that which operates in puerperal cases could be invoked in this form of recurrent abscess In one nonpregnant woman stasis of secretion in a lactiferous duct was followed by plasma cell mastitis The surgeon incised the area under the impression that he was dealing with abscess No organisms were found. Some months later the wound broke down with discharge of pus This time the diagnosis was abscess Apart from infection following incision of an area of plasma cell mastitis, stagnant secretion in the lactiferous ducts is particularly vulnerable to invasion by organisms from the skin Caswell, Taylor and Burnett (1956) in a report on six cases of mammillary fistula call attention to this factor In all six women the nipples were inverted—a common finding in secretory disease —and infection appeared to originate "on the basis of maceration and cellulitis involving the cutaneous and glandular structures in the groove of the inversion of the nipple

Inflamed secretory cysts are not uncommon although seldom diagnosed as such. The difficulty encountered in most cases is to decide whether the inflammation is bacterial or chemical. In most of our specimens no cultures were asked for by the surgeon and in long-standing lesions the pathologic features were often not decisive The possibility that some inflamed secretory cysts become infected and progress to abscess needs investigation. In a fully developed abscess the original cyst wall is destroyed and evidence of etiology is not forthcoming A review of our material

emphasized the necessity of finding criteria other than in the lesion itself if the problem was to be solved. Two separate approaches were tried. The first was to search the excised specimen for characteristic ducts filled with colostrum-like cells and lined by secretory epithelium. These were sometimes present, but in most cases the surgeon had confined removal of tissue to the abscessed area, or had done simple incision and drainage and adjacent tissue was not available.

The second approach embraced a wider field. If the hypothesis that all intramammary abscesses have their origin in stasis of secretion is correct, a clue to the underlying condition might be found in the contralateral breast. Such an investigation would be capable of demonstrating secretory disease with or without cysts, puerperal states, and any other lesion which would result in stagnation of secretion. Accordingly nineteen cases of intramammary abscess in which satisfactory films of both breasts were available were studied. Twelve were nonpuerperal, secretory disease was present in ten women, four of whom had nipple retraction. Two women of this group had retracted nipple without secretory disease. Of seven puerperal cases, three had nipple retraction This was in sharp contrast to our cases of superficial abscess, none of which presented lesions in the opposite breast.

THE DIFFERENTIAL X-RAY DIAGNOSIS OF BENIGN BREAST LESIONS

The trained radiologist recognizes soft tissues not merely by their outlines, but also by differences in density in different tissues. In the breast, variations in density are relatively slight. The coefficients of absorption of the component structures are close to that of water and can only be brought out by meticulous attention to technic. On the x-ray film air and fat are almost translucent, water is less translucent, having a coefficient of linear absorption of 1 0 compared to 0.92 for fat The figure for transudates is 1.008, for blood and for pus 1.06 (Melot 1947). Cysts filled with clear albuminous fluid are discerned with relative ease, especially when large The thickness of the fluid layer and the pushing aside

of other tissues in the area enhances their visibility These advantages do not obtain to the same extent near the base of the breast, small cysts in this region are hard to discern. Cysts containing blood or pus, as in chronic abscess, are easy to see provided the outlines are not masked by inflammatory reaction around them. Fibrous tissue has a coefficient of 1.2 In practice its opacity varies according to the amount of water it contains and with its physical and chemical makeup On a film the thickness of an area of fibrosis often decides whether other structures such as cysts will be masked by it.

The cellular component of the breast has about the same density as the fibrous tissue and is not distinguishable from the fibrous parenchyma. Owing to difference in thickness at the base and apex, uniform exposure of the entire organ is not possible without special apparatus and technics Skin and nipple are well seen in otherwise underexposed films, but are often blacked out when sufficient exposure is given to define structures in the gland itself The fibromuscular pad is situated just below the nipple. It is ordinarily clearly visible. The lactiferous ducts are seen to enter the pad and are then lost to view Absolute increase in density is found in many scirrhous carcinomas Other tumors have relatively increased density because in most cases their structure is more compact than that of the breast in which they lie. Very small growths can be discerned in postmenopausal atrophic breasts because they lie in a bed of fat. The glandular breasts of younger women contain a smaller proportion of adipose tissue and tumors are correspondingly more difficult to define. In immature breasts with no fat the tumor may have exactly the same density as the surrounding parenchyma. Unless the margin is seen, diagnosis may be impossible. The presence of a "halo around a fibroadenoma and of a perifocal zone in which breast structures are absent in carcinomas are both very helpful. Calcium is the most radiopaque material seen in the breast. It is a common component of tumors and of great assistance in diagnosis The calcified particles are dead white on the film and can be recognized even when they are at the limit

of visibility. A hand lens is useful for their identification when they are very small as in some duct carcinomas

Melot made a thorough investigation of the permeability of soft tissues to x-rays. Taking the knee as a starting point, she found as others had done, that when the same x-ray technic is used in different individuals, equal thicknesses of soft tissues do not give equal clarity of delineation. Each technical factor was investigated in turn and the results of each variation were recorded photometrically using the x-ray film The author showed that the density of soft tissues varied with their water content. They differed in children, adults and old people. The same technical principles were successfully applied in the study of the anatomy and pathology of the breast. As in a limb so in the breast, measurement of the thickness of the tissue to be examined does not ensure good visualization; exposure must be judged by the firmness or flabbiness of the organ rather than by its size. Consideration of age and of physiologic state is of paramount importance in the achievement of technically perfect films of the mammary gland

Difficulties in x-ray diagnosis stem chiefly from two sources: (a) An abnormal area is overlayed by other structures and is incompletely visualized Most problems of this type can be resolved by technical modifications. The patient's position may be changed or different technical factors can be tried. Re-examination of the patient at a different stage of the cycle is sometimes effective. (b) The lesion is visualized, but differential diagnosis is difficult or impossible. The radiologist should have this possibility clearly in mind and know when an exact diagnosis cannot be given Many pitfalls can be avoided by a thorough grounding in pathology. Given this training, the radiologist is saved from making impossible diagnoses. Proper attention to history and clinical findings prevent many mistakes. The necessity for knowledge of the normal breast has already been stressed.

For the reader's convenience the principal sources of error in the x-ray diagnosis of benign lesions are emphasized in the following paragraphs and summarized in table I

TABLE I

X RAY DIAGNOSIS OF BENIGN BREAST LESIONS

Adenosis	Mazoplasia Fibrosa	Mazoplasia Cystica	Fibro-adenoma	Secretory Disease	Mastopathy	Intraductal Hyperplasia	Papilloma
Multiple bi lateral often circum scribed opacities of glandular density	Compact homogenous dense breast bos-elated surface.	Single or multiple rounded sharply de-fined opaci ties.	Bosselated or round sharply defined opacity often shows halo diffi cult to visualize in dense breasts occasionally coarse calci fication.	Dilated lactiferous, sometimes other ducts dense fibrosis in subareolar area, calci fication in duct wall. Plasma cell mastitis irregular poorly out lined opacity with extensions in line of trabeculae	Mixture of any or all forms of dysplasia.	Irregular dilatation of ducts, punctate calcifica-tions, even when ducts are not seen.	(*a*) Intra ductal varicose distension of ducts. (*b*) Intra-cystic resembles solitary cyst but more opaque.
DIFFERENTIAL DIAGNOSIS							
Physiologic hyperplasia lactation involution, plasma cell mastitis early lobular carcinoma.	Normal immature breast	Fibro-adenoma (not always possible) other cystic lesions cir cumscribed carcinoma.	Cysts sarcoma circum-scribed carcinoma.	Carcinoma papilloma intraductal hyperplasia other forms of mam-mary dysplasia traumatic fat necrosis	Carcinoma.	Carcinoma benign papilloma secretory disease.	Occasion-ally secre-tory disease mazoplastic or other cysts fibro-adenoma.

1. *Adenosis.* Irregular lobular hyperplasia is extremely common. Minor grades of the disorder are often difficult to distinguish from normal breast tissue. For example, in the later stages of lactation involution, fluffy patches are seen which could only be interpreted in the light of a history of parturition some time previously.

In cases of doubt the first consideration is comparison with the normal glandular type of breast. In generalized adenosis the basal opacity and trabeculae are broadened and much more fluffy than in the normal breast. The presence of additional fluffy opacities would be decisive for adenosis. The coexistence of adenosis, cysts, and fibroadenoma must not be forgotten Very careful search must be made for clusters of minute calcified particles which could betoken intraductal hyperplasia, carcinoma in situ, or duct carcinoma. A spiculated opacity with disruption, however slight, in the perifocal zone should be examined with greatest care. At times the beginner will be confused by small stellate opacities which mimic early scirrhus, but are in reality distorted trabeculae or small fibrous scars. They must not be confused with the tentacles streaming from the body of a cancer The presence of dilated ducts, especially clusters of small ducts, need explanation They are not part of adenosis, but could be associated with intraductal hyperplasia (fig. 164).

Adenosis must be distinguished from early lobular carcinoma and from early cases in which the tumor shows a lobular mode of spread. In both the diagnosis is extremely difficult; on the x-ray film the carcinomatous areas resemble hyperplastic lobules. At the present time our experience with these rather rare types of growth is small.

2. *Mazoplasia Fibrosa.* Generalized mazoplasia fibrosa is uncommon in our experience. These breasts contain little fat and what has been said of immature breasts applies here The chief difficulty is to visualize accompanying fibroadenomas. Malignant tumors are fortunately rare, but are extremely hard to recognize (fig 177)

3 *Mazoplasia Cystica* is difficult to distinguish clinically from adenosis, but is easy to diagnose on the x-ray film provided the

cysts are seen. At times the cysts are masked by accompanying adenosis If the diagnosis is in doubt additional roentgenograms should be taken at another, preferably postmenstrual, phase of the cycle. The round sharp margin of cysts is so distinctive that the diagnosis can usually be made if only a part of the cyst is showing

4. *Fibroadenoma* The chief difficulty is that fibroadenoma occurs in young dense breasts The tumor is easy to feel and difficult to see. However, with modern x-ray apparatus this difficulty has been largely overcome. Sometimes it is necessary to push the tumor to the surface and take its x-ray picture in profile The distinction from a cyst cannot as a rule be made on the x-ray film and should seldom be attempted When a fibroadenoma is developing from adenosis, a sharp margin is present only on one side of the mass (fig. 79) Coarse calcification is seen in long-standing fibroadenomas It is a rather striking phenomenon and must not be allowed to distract the eye from more serious lesions such as carcinoma (fig 170)

5 *Secretory Disease* In making a diagnosis of secretory disease the life history of the disorder should be borne in mind. While all stages have not been completely worked out, enough is now known to alert the radiologist as to what to expect and what not to expect at different ages In young women it often begins as an intermittent milky discharge following lactation The lactiferous ducts will then be slightly dilated, but not otherwise abnormal The diagnosis may be made if the mammary parenchyma behind the ducts has a ground-glass texture similar to that seen in pregnancy or lactation In older women the chief changes are in the ducts, the lactiferous ducts being especially affected Two things are to be looked for the first is thickening of the wall, the second is dilatation, tortuosity and sometimes beading of the ducts Besides dense fibrosis, long-standing cases of secretory disease show a variable amount of calcification along the line of the ducts When dilatation and tortuosity are present the distinction from multiple intraductal papillomas is difficult, if not impossible, to make on the x-ray film alone. A point to remember is that the subareolar area may not be

affected in papilloma whereas it is the chief site of the lesion in secretory disease. Nipple retraction occurs in older women with secretory disease, but is very rare in papilloma Of considerable assistance in diagnosis is the fact that secretory disease is nearly always bilateral. Nipple retraction, often present in long-standing cases, may be more marked in one breast, but is to be expected in both and is more easily seen on the film than in the patient.

6 *Plasma cell mastitis*, the complication which brings most patients to the doctor's office, needs considerable care in diagnosis On the x-ray film it appears as an irregular opacity or multiple opacities. The lesion varies considerably in extent in different cases and may be bilateral. The margins are irregular, sometimes stellate, and merge into the parenchyma. The area seen on the x-ray film is larger than that measured clinically, a very important point in differentiation from carcinoma The presence of secretory disease in both breasts is of considerable assistance in the diagnosis and will distinguish plasma cell mastitis from adenosis. Carcinoma and abscess are the two most important conditions to consider in differential diagnosis. With regard to carcinoma, onset with pain is unusual, but not as uncommon as is often thought. It is a notable feature in inflammatory carcinoma. In plasma cell mastitis onset with pain and swelling is the rule, but there are exceptions The swelling of plasma cell mastitis tends to decrease in a few days, but we have encountered one carcinoma in which this happened and of course carcinomas may shrink with testosterone medication. The wary radiologist will scrutinize the x-ray film with meticulous care The discrepancy in clinical and x-ray size has already been noted. Equally important is the observation that the extensions in plasma cell mastitis spread along the trabeculae, in carcinoma they often cut across them A carcinomatous mass is usually denser and more sharply defined than the tumor of plasma cell mastitis. The presence of characteristic secretory disease in the contralateral breast may help to put the radiologist wise to the possibility of plasma cell mastitis, but by no means excludes carcinoma

7 *Abscess and chemical or plasma cell mastitis* have much in

common, in fact most intramammary abscesses originate in foci of plasma cell mastitis Differentiation on the x-ray film is often difficult, but extremely important since the treatment is by no means the same. The chief points in favor of abscess rather than chemical mastitis are thickening of the skin from edema and extreme vascular engorgement. Signs of secretory disease may be present in both, their absence points to abscess

8 *Inflamed cysts*, either mazoplastic or secretory, often resemble circumscribed carcinomas On the x-ray film the margins of the lesion may be irregular or even spiculated. The radiologist should report such cases as suspicious of carcinoma and let resection decide the issue.

9 *Mastopathy* (*Schimmelbusch's Disease*) is diagnosed when a mixture of benign lesions is seen on the x-ray film. Individual dysplasias cannot always be distinguished, but however complicated the appearances, exclusion of carcinoma is necessary and nearly always possible. Even if definite diagnosis cannot be made the radiologist can play an extremely important part by insisting on biopsy of a suspicious area.

The busy radiologist is often tempted to shelve the differential diagnosis of dysplasia and be content to label a lesion benign or malignant. A step further on the downward path is to save trouble by having a rubbish heap on which to discard conditions which require some effort to elucidate their real nature If the rubbish heap is simply labeled "dysplasia ' no great harm is done. Further elucidation of the type of lesion can be made if required In the past the popular rubbish heap was 'chronic cystic mastitis " Now "fibrocystic disease' has come into vogue Kaier's "fibroadenomatosis' is an improvement, but includes conditions such as intraductal hyperplasia which are better separated. It is true that a mixture of adenosis and hyperplastic fibrosis is rather common. The word adenofibrosis might be used to designate this provided the meaning is clearly understood. In brief, technical terms must convey a definite meaning To use them in any other way puts an end to scientific advance.

PART III

Neoplastic Disease

Neoplastic Disease

INTRADUCTAL HYPERPLASIA AND PAPILLOMA

INTRADUCTAL hyperplasia is not necessarily precancerous, in point of fact most examples are benign, on the other hand, the reverse proposition that most carcinomas have their origin in intraductal proliferation is certainly true Hence careful study is indicated in all cases of this disorder

Grossly, all stages of dilatation of ducts are encountered, depending on the amount of epithelial proliferation within them. Some degree of ectasia is always present The earliest visible lesion appears merely as a translucent pale or dark red spot. Well-developed papillomas cause focal distension and where they are multiple the ducts are characteristically beaded. Epithelial hyperplasia without true papilloma may cause irregular dilatation depending on its severity and the extent of the lesion, the contents of the duct are soft and often bloodstained In many cases of irregular dilatation a mixture of unorganized cell proliferation and papilloma is encountered.

Slight heaping up of epithelial cells here and there is a concomitant of many dysplasias and is not usually significant. It may be disregarded provided the tissues are otherwise well developed and well differentiated. In normal breasts proliferation indicates the growing point of a ductule or the budding of a new lobule Larger collections of cells must be judged according to their degrees of differentiation and organization. For this purpose classification is useful, but it must be realized that hard and fast lines do not exist in breast pathology Classification is only a scaffold, but as the experience of the investigator increases more and more cases will be placed in their proper categories

1 Fully differentiated secretory epithelium. Masses of vacuolated epithelial cells are seen in the ducts in secretory disease. They degenerate rapidly and appear as colostrum corpuscles Since they

are fully developed they cannot divide and cannot become carcinomatous Occasionally inflamed granulation tissue growing into the lumen of the duct is found in the form of a polyp covered by these cells (fig. 157).

2. Nonsecretory epithelial cells (figs. 158, 159) When fully developed these cells have vesicular nuclei and pale cytoplasm which often contains granules. In the first half of the cycle the



FIG 157 Intraductal polyp from a case of secretory disease. The polyp projects into a dilated duct It consists of granulation tissue in which are numbers of large clear partly degenerated cells resembling the colostrum corpuscles seen in lactation Most of them are in the epithelial layer covering the polyp The lining epithelium of the duct presents similar secretory cells The lumen contains fatty debris and shadows of colostrum cells Scattered inflammatory cells are seen in the polyp and in the tissue surrounding the duct.

nuclei are smaller and darker and the cytoplasm is less abundant. The nuclei become columnar as they impinge on the surface With routine staining methods a real difficulty is to distinguish normal epithelial cells from cells of a precancerous hyperplasia. The best test is to look for myoepithelial cells If myoepithelium is absent or poorly developed suspicion of a possible precancerous lesion should be entertained.

3 Benign papillomas The textbook papilloma is described as consisting of a core of fibrous tissue covered by epithelium. The way in which such structures are formed is seldom mentioned, but many specimens show successive stages which are fairly easy to follow (figs 158, 159) A papilloma is a growth of epi- and myothelium into the lumen of a duct. At the beginning there is a jumble of immature elements indistinguishable from cells seen in the earliest stages of pregnancy (fig 158A) Soon, just as in pregnancy, the primitive myoid cells show blunt processes and striated cytoplasm and the epithelial cells arrange themselves in rows In actual practice differentiation is always seen somewhere in the section so that the benign nature of the lesion is assured. At this point the difference between papilloma and pregnancy begins to emerge. In both, ductules may appear, but pregnancy is concerned with the formation of lobules Even if the proliferation begins within a duct the new lobular buds grow outward The myoid layer surrounds the epithelium in orderly fashion and forms normal intraductal connective tissue. In papilloma, on the other hand, there is defective organization. Growth takes place into the lumen of the duct. Ductules may be present, their epithelial lining may be normal, but they grow in haphazard fashion and are not organized into lobules The proliferating myothelium is covered by a continuous layer of epithelium and gradually undergoes conversion to fibrous tissue. At this stage there may be indications that active growth has ceased. In some papillomas a further stage of hyalinization is seen, the vascular supply is cut off, the epithelium degenerates, and all that is left is a hyaline knob projecting into the duct. In other papillomas the myoid core undergoes mucoid degeneration. The

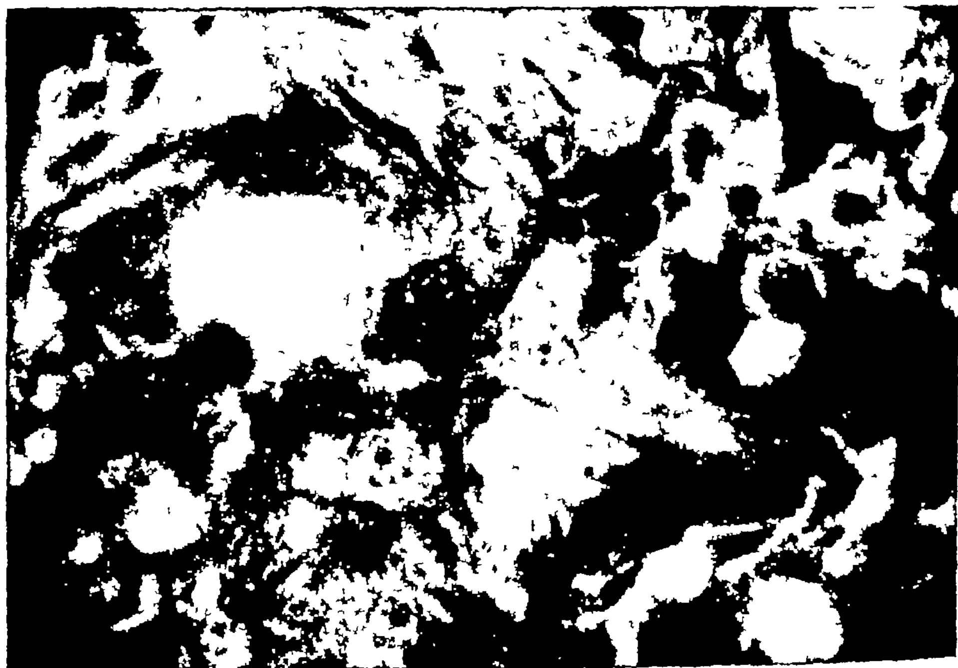


FIG. 158. A

B

FIG 158

C

D

papillae then resemble those seen in benign papilliferous cysts of the ovary.

In another form of papilloma the tumor has the structure of sclerosing adenosis (myoid sclerosis) (fig. 160). The mass is formed in great measure by proliferating myoepithelial cells. This tumor has the same fate as myoid sclerosis outside a duct—its final form is a fibrous scar. Intraductal fibromas may originate in this way.

Intracystic papillomas are often given a separate classification, but the distinction is more of a clinical convenience than a true difference in type or derivation of the tumor. Intracystic papilloma is generally thought of as a papilloma arising within a previously formed cyst. It is more probable that cyst and papilloma arise together. The hyperplasia which gives rise to papilloma in these cases is likely to be part of a general hyperplasia of the wall of the duct. A duct which has become cystic rarely discharges its contents via the nipple and it is likely to be further distended by serous exudate or hemorrhage from the papilloma Papillomas could scarcely arise from the simple cysts of mazoplasia since such cysts are lined by atrophic cells. The largest papillomatous cyst we have encountered occurred in a woman of fifty-nine years. A mass had been present in the lower outer quadrant of the right breast for many years. One year before, following trauma, there was con-

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FIG. 158 C 151. Multiple benign intracystic papillomas following prolonged estrogen medication. Age fifty-one years. Movable mass 3 cm diameter just medial to areola noted five weeks. For the past two years the patient was given monthly injections for "change of life" A hysterectomy was done for persistent vaginal bleeding The endometrium was extremely hyperplastic and succulent. X-ray film showed a very clearly defined cyst in the region of the tumor.

A and B. *Successive stages in formation of benign papillomas.* Very active proliferation of immature epithelial and myoepithelial cells. Note large vesicular nuclei, prominent nucleoli and striated cytoplasm of myoepithelial cells They resemble those of early pregnancy. Oil immersion, × 1000

C Low power view to show a further stage of myothelial development in the core of the papilloma, × 100

D *Endometrium—persistent estrin phase*

siderable swelling accompanied by brownish discharge from the nipple. This subsided until two months previous to admission when the area again became swollen and discolored and grew progressively larger On examination a huge swelling with discoloration of skin was noted. The x-ray film showed an enormous biloculated cyst The day before operation the skin ruptured with profuse hemorrhage. Operation revealed the hemorrhagic cyst with bunches of benign papillomatous growth springing from the wall (fig. 161) In this case the size of the cyst was due to hemorrhage from the tumor

4. An adenoma rather than a papilloma may grow within a duct. Its benign nature may be recognized by the fact that the tumor ductules possess a definite intraductal fibrous layer Much more difficult to assess are tumors in which ductlike structures are formed by typical epithelial cells, but no other cellular elements or stroma are present. Regularity in size and arrangement of the cells suggest a benign growth. Evaluation of surrounding structures and of the section as a whole is important. Obviously one area of intraductal proliferation in a section is not a clinical carcinoma The question to be answered is whether the patient is in danger of developing a carcinoma later We have noted that dysplasias tend to remain true to type over many years If a lesion is really 'precancerous,"—and judgment on this point is extremely difficult, then the patient must be watched and any subsequent mass must be dealt with promptly If on the other hand the lesion is benign and has occurred in the course of an obviously benign dysplasia, the recrudescence of the dysplasia need not cause anxiety

5 Precancerous hyperplasia and carcinoma in situ (figs 162, 174) Besides the adenomatous form just discussed there is massive proliferation of cells which, although uniform, not increased in size, and of normal nuclear pattern, show no tendency to organization. They are not cancer, but their interpretation demands the greatest caution. In some cases they probably degenerate and cause no further trouble. In others, the cells may show some lack of uniformity and in yet others all degrees are found, up to the

FIG 159.

A



B

atypical cells of 'carcinoma in situ." For evaluation of the lesion it is essential to know the extent of the tissue involved and as many blocks as is necessary should be cut. Very careful search must be made for the existence of a small carcinoma. Roentgenography must not be neglected for a good x-ray film may be invaluable in tracking down suspicious areas (fig 193)

In carcinoma in situ the cells are large and are unequal in size The nuclei are large, occasionally enormous, and immature with prominent nucleoli (fig 174) Small clusters or nests of immature cells are seen pushing the older cells aside. Attempts at organization in the form of ductlike structures are found in the midst of the amorphous jumble, but they are obviously abnormal. Calcification of degenerate epithelial cells is occasionally found (fig 175) The behaviour of the myoid is extremely interesting At the site of the proliferation myoepithelial cells are absent or hard to find (fig 174B) When seen they are usually old cells already at the fibrocyte stage. In a few specimens immature, partly developed myoepithelial cells are seen in the area of growth. They are abnormal and seem to represent a differentiation of tumor cells toward the myoepithelial side. At a little distance from the tumor the picture may be quite different. In some cases there is tremendous proliferation of myoepithelium, apparently in an effort to prevent the spread of the growth (fig 174C) Myoepithelial hyperplasia of this character does not have the same benign connotation as in adenosis where it is a part of the lesion itself On the contrary, it is circumstantial evidence of the malignancy of the tumor Jackson and Orr

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FIG 159 C 32 Multiple benign papillomas. Age twenty-seven years Discharge from right nipple, sometimes bloody sometimes clear for three years A dilated duct was palpated in the upper outer quadrant extending to the nipple. The x ray diagnosis was papilloma. One smear of nipple discharge failed to reveal cells. Pathologic section showed stages of involution of benign papillomas Several were undergoing hyaline degeneration sometimes with early calcification of the hyalinized tissue.

A. Hyalinization in the stalk of a benign papilloma.
B Mucoid degeneration in the core of a papilloma.



FIG. 160. Intraductal myoepithelial tumor The myoepithelial cells predominate and are remarkably well developed The tumor has the structure seen in sclerosing adenosis (myoid sclerosis).

(1957) have called attention to thickening of the intraductal connective tissue in precancerous epithelial hyperplasia Histologic investigation shows that the change is due to increase in elastin and collagen in the subepithelial tissue We agree with the authors on the importance of this sign. Our own observations suggest that elastosis and collagenosis follow degeneration of the hyperplastic myoid.

Another form of carcinoma in situ resembles duct carcinoma in everything except infiltration of the surrounding tissues (fig 175) Groups of ducts are lined by a collar of rather uniform carcinoma cells which make no attempt at organization. The lumen is occupied by necrotic material, often with small foci of calcification It is our experience that carcinoma of this type grows extremely slowly and may remain in situ for a very long time. Figure 175 is from an old woman who could give no history, but had a nodular area palpable just above the left nipple. On section the tumor measured 3 × 1 3 cm. and was formed entirely by ducts with thick, hyalinized, sometimes calcified walls The lumen was lined by many layers of small carcinoma cells and contained necrotic, partly calcified material. This material was discharged via an extremely retracted nipple. Serial slices as well as paraffin sections were made of the entire area and in spite of the extent of the lesion no infiltration was discovered. Apparently the fact that the duct contents found an outlet via the nipple, coupled with limitation of spread imposed by extreme hyalinization of the outer part of the walls, prevented dissemination of the cancer

Carcinoma in situ is clinically benign. Until growth invades the adjacent structures it does not metastasize (Greene, 1939) It is the last stage of intraductal hyperplasia before frank carcinoma develops

6 Malignant papilloma. Haagensen states that most papillomas are benign and remain so We fully agree. The corollary is that malignant papillomas are so from the start. As a rule the tumor is easy to recognize microscopically, even if infiltration is not present. Grossly, it is soft, friable and hemorrhagic.

Clinically, papillomas as well as some intraductal hyperplasias betray their presence by nipple discharge, often intermittent and usually bloody As a rule, the blood is bright red. When blood is not present the discharge is serous A tumor may or may not be felt. According to Haagensen, if no tumor is palpable the lesion is benign, but the x-ray film has shown that the presence or absence of a mass is not a safe guide. The reverse proposition that palpable



B



A

Fig. 161.

papillomas are malignant is of course not true. Benign papillomas are most easily diagnosed by examination of smears from the nipple discharge Typical epithelial cells are seen singly or in clumps Sometimes broken off papillae can be recognized. The diagnosis is then clear However, it is important to realize that several examinations may be necessary before diagnostic cells appear One woman, aged sixty-three years, complained of serous discharge from the right nipple for three weeks, smears were made at two- to three-week intervals thereafter After three months a piece of benign papillomatous tissue was seen. Two months later she had a bloody discharge, she then consented to operation. The ducts in the right upper outer quadrant contained numerous benign papillomas

Other forms of intraductal hyperplasia may also be signalized by bloody nipple discharge, and since hyperplasia and benign and malignant papillomas are sometimes found in close juxtaposition in the same duct, carcinoma cells are not always apparent. Interpretation of the smear may be confusing, but as in papilloma, if enough samples are taken the diagnosis can usually be made.

Leborgne uses contrast mammography with considerable success in the diagnosis of papilloma. A single intraductal mass may be accurately outlined and with suitable intruments an intraductal biopsy may be taken. In the hands of a competent operator the procedure is safe and need not cause pain.

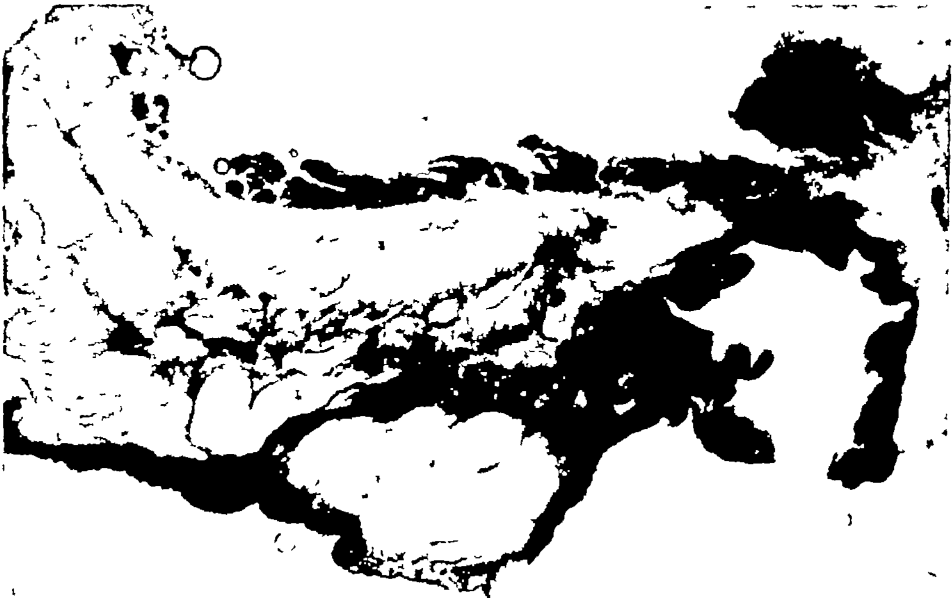
Papillomas have no counterpart in the normal mammary gland In this they differ from the dysplasias Fibroadenomas are called tumors, but are in reality focal dysplasias Cysts are mimicked by

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FIG 161 C 40 Intracystic papillomas. Massive hemorrhage with rupture through skin. Age fifty nine years.

A. X ray film taken before rupture shows a large bilocular cyst in the right lower outer quadrant.

B Slicer section showing part of the cyst. The cyst wall extends to the skin which was ruptured at this point. Several papillomas are seen projecting from it. Many more were present but they were disrupted by hemorrhage.





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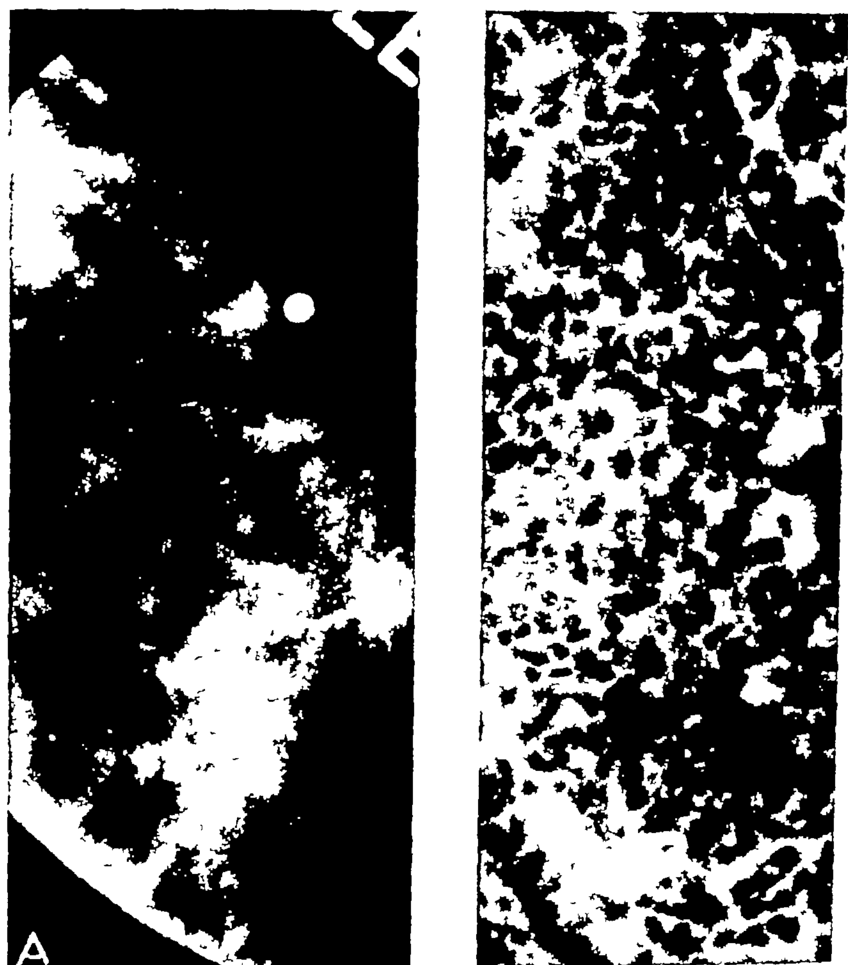


FIG 162. C 1028 Precancerous intraductal hyperplasia. Age thirty-seven years Discharge from left nipple one year. Operated on for a similar discharge from right nipple six years before. The patient was hospitalized for a recurrent mass in the left upper outer quadrant No tumor was felt in the nipple area

A. X-ray film shows an area of adenosis at the site of the marker. A small opacity is seen subjacent to the nipple It contains fine calcified particles showing lack of polarity.

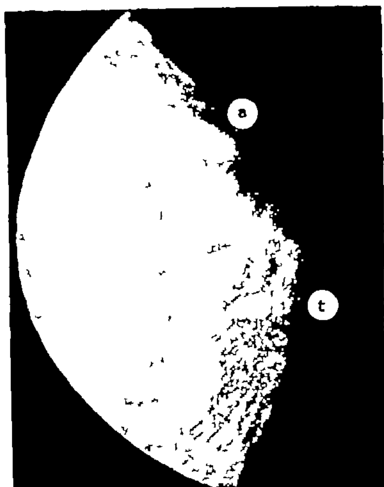


FIG 162 A

B Microphotograph shows ducts filled with cells Epithelial cells are uniform, but organization is poor and no differentiation of myoepithelium is visible in the tumor

A Drawing from x ray film. a," clinically palpable mass due to adenosis, "t," tumor beneath the nipple.

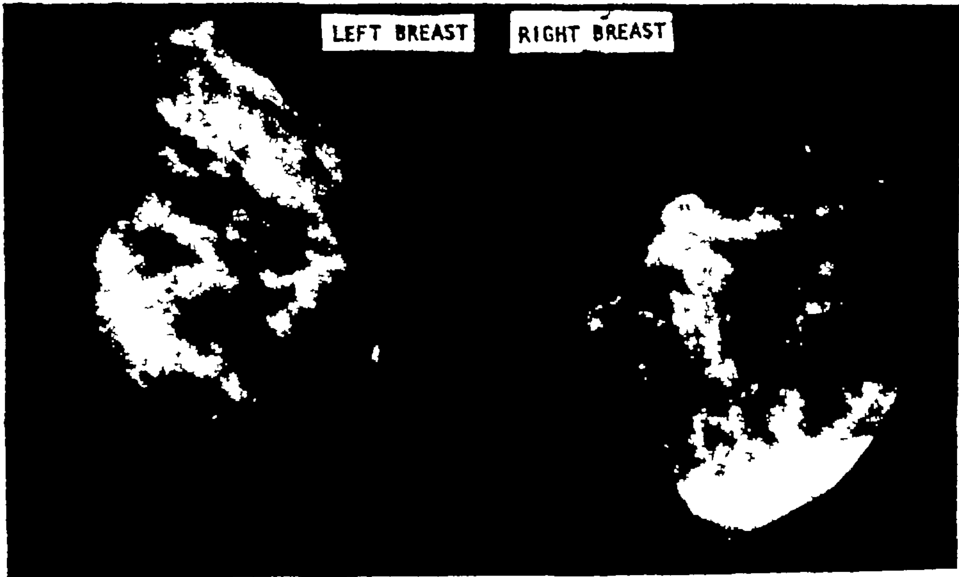
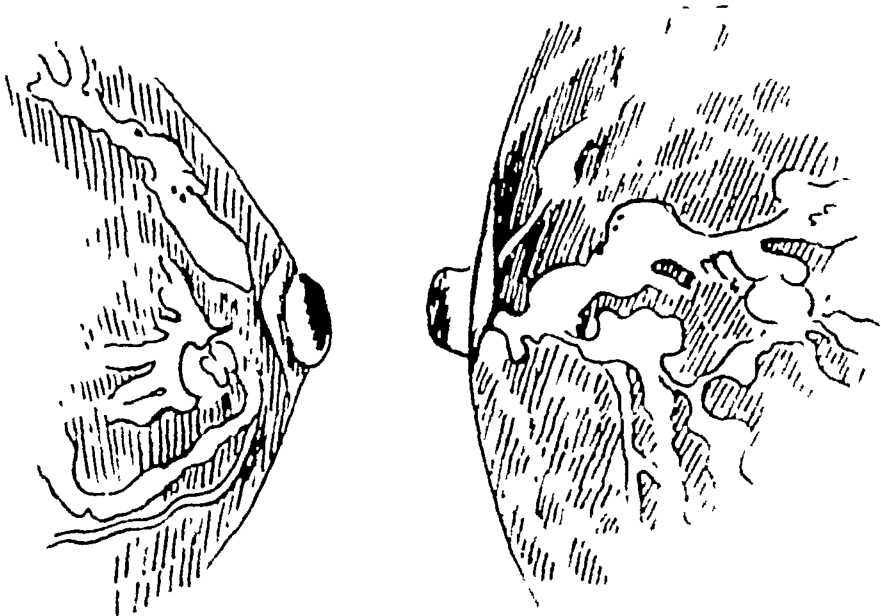


FIG 163. A



A′

the developing adolescent breast. Papillomas are never physiologic and must therefore be classed as neoplasms Nevertheless hormone imbalance is a significant factor in their etiology Our attention was first called to the part that hormones might play by the case of a woman with multiple benign intracystic and intraductal papillomas who had been receiving large doses of estrogen for two years (fig 158) An analysis of twenty-two cases has shown evidence of hormone imbalance in seventeen. Eleven had received estrogenic hormones in significant doses Thyroid enlargement was present in five. An unusually high proportion gave a history of breast carcinoma in the next of kin

X-ray diagnosis of papilloma while often difficult is possible in most uncomplicated cases On the x-ray film a single papilloma will produce an opacity in the course of a duct. As long as no invasion of adjacent tissue is seen the only way to decide whether the tumor is benign or malignant short of operation would be by means of a nipple smear The x-ray film in multiple papilloma shows beaded varicose ducts leading to the nipple (fig 163) In most cases the ducts are clearly discerned They might, however, be confused with similar tortuous ducts seen in secretory disease. Both conditions may show opacity beneath the nipple, but in secretory disease fibrosis is more marked. The coexistence of multiple papillomas and unorganized epithelial hyperplasia must not be forgotten. If there is general irregular dilatation of ducts accompanying discrete swellings the more serious diagnosis of intraductal hyperplasia should always be made. Intracystic papillomas can only be suspected on the x-ray film if the cysts are unusually dense (fig 161)

FIG 163 C 415 Bilateral intraductal papillomas. Age thirty-nine years. Discharge from both nipples six years Premenstrually the discharge became bloody At operation dilated ducts containing benign papillomas were found in both breasts.

A. X rays show varicose swellings of ducts in both breasts Scattered calcified particles are contained in the papillomas.

A Drawing from x ray films



FIG. 164 N 405. Benign intraductal hyperplasia.

Age forty-one years. Asymptomatic On routine x-ray examination a lesion was noted in the left upper outer quadrant. The diagnosis was ectasia of small ducts and the patient was asked to return in six weeks.

An x-ray film taken six weeks later shows an opacity (arrows) with irregular, poorly defined margins The lesion was slightly larger than when first seen X-ray diagnosis was intraductal hyperplasia, or possible early carcinoma. The area was excized and after some hesitation the pathologist reported the lesion benign In this case diagnosis of intraductal hyperplasia was made on the x-ray film in spite of the absence of punctate calcifications.

Intraductal hyperplasia (figs 162, 164), while not invariably recognizable on the x-ray film, can be suspected in many cases and sometimes definite diagnosis may be made. Obviously considerable skill and experience on the part of the radiologist is a *sine qua non*. From the point of view of prevention of cancer in the individual patient the diagnosis is the most important that he can make. The larger ducts are dilated and of irregular caliber, but definite beading is more likely to be associated with papilloma. Small ducts may not be visible. The most significant sign, although not always present, is calcification. The calcifications resemble those of duct carcinoma. They may occur in tiny clusters or in rows Their detection requires sharp eyesight and meticulous examination of the film, the more so as they may occur away from a palpable mass and other lesions are apt to attract the attention of the radiologist. Occasional minute calcifications are seen in benign papillomas, but fairly numerous calcifications, especially in the absence of a palpable tumor, suggest carcinoma in situ. If the presence of a few small calcifications is accompanied by disruption of breast pattern, malignancy whether intraductal or extraductal is suspected, but differentiation between benign proliferation, precancerous proliferation, carcinoma in situ, and actual carcinoma may be impossible. In the absence of calcification an abnormal breast pattern is usually not diagnostic, but if the lesion is focal and no similar condition is seen in the opposite breast it demands investigation The x-ray film is then of service in designating the site for a biopsy, a mandatory procedure under these circumstances whether the lesion is palpable or not.

CARCINOMA

From the practical standpoint carcinoma is by far the most important lesion found in the breast. Almost all others derive their importance from their relationship to it. The clinical and pathologic manifestations of cancer are so varied and its onset so insidious that malignancy is frequently not diagnosed until it is too late



A B

Fig. 165.

to save the patient. On the other hand many surgeons and pathologists, knowing this, are in the grip of cancerophobia and any and every lump is treated by prompt removal without due consideration of diagnosis

Early and accurate diagnosis is therefore all-important and our experience has shown that in the hands of experts the most reliable adjunct to clinical acumen is the x-ray film. A good roentgenogram reveals not only the nature of a clinically palpated mass, but often uncovers the existence of a previously unsuspected tumor The radiologist must be thoroughly conversant with the criteria of malignancy and be likewise familiar with the normal breast and with benign lesions He must also have a good working knowledge of breast pathology Thus equipped he will seldom have difficulty in reaching a correct decision. In some cases no definite conclusion is possible, but he will be able to point out an area of probable carcinoma where biopsy should be performed. Needless to say, the case history should always be available. There are some who are foolish enough to withhold information on the grounds that the radiologist will be biased. This shows remarkable ignorance of the possibilities and limitations inherent in all forms of diagnosis In the patient's interest all available information should always be brought under review Every circumstance must be given its due weight and no point can safely be overlooked. Should the x-ray

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FIG 165 C 280 Advanced scirrhous carcinoma. Age sixty-five years Mass in left breast eight months, it arose at the site of a puerperal abscess which had healed thirty seven years before.

A. X ray film, cephalo-caudad view, shows a fairly large spiculated opacity The spicules cut across the line of the trabeculae. No normal breast structures are seen in the perifocal zone. A fibrous band extends from the tumor to the nipple which is markedly retracted.

B Slightly reduced slicer section from the same case, but cut at a different angle. The tumor tentacles extend to the muscle and skin as well as to the subareolar area. The skin is intracted and the lactiferous ducts distended. Their walls are thickened. The nipple is not present, but a part of the thickened and retracted areola is seen.

A

B

Fig 166

appear to contradict clinical or pathologic evidence, a further review is necessary and additional films should be taken when indicated. When the above conditions are observed, our present experience shows that we can make a definite diagnosis of benign or malignant lesion in 80 per cent of all examinations (table II)

TABLE II

X RAY DIAGNOSIS IN 1,500 CONSECUTIVE EXAMINATIONS OF THE BREAST

Accuracy Determined in 536 Operated Cases

X Ray Report	No Cases	Operated	Benign	Malignant	Accuracy percentage
Normal	168	11	11	0	100
Benign	919	234	229	5	98
Malignant	118	108	2	106	98
Probably benign	173	91	83	8	91
Possibly malignant*	122	92	44	48	52
Total	1,500	536	369	167	89

*Cases considered suspicious but not typical of carcinoma Surgery was urged in all cases. "Benign findings at operation includes six cases of severe or precancerous intraductal hyperplasia.

In those cases where operation follows, accuracy is 98 per cent or better In the remaining 20 per cent of cases, the x-ray diagnosis is of more limited value, and accuracy, when checked against operation findings, is correspondingly lower Not all carcinomas

FIG. 166 C 449 Scirrhous carcinoma. Age fifty-one years. Mass right breast noted one year

A. X ray film shows a large spiculated tumor surrounded by enormous veins. There is loss of breast architecture in the perifocal zone. The nipple is retracted.

B Slicer section of the tumor

LEFT BREAST RIGHT BREAST

FIG. 167 A



B

are visible and a negative opinion should only be accepted after careful appraisal of all the pertinent factors Clinical accuracy in the diagnosis of breast lesions is seldom better than 70 per cent, a figure which includes doubtful as well as definitely diagnosed lesions and the surgeons associated with us now insist that x-ray studies be part of the routine work-up of a case. In practice, x-ray failures are often correctly diagnosed by the surgeon and vice versa. When surgical acumen is combined with x-ray studies a correct preoperative diagnosis may be achieved in 95 per cent of cancers (table VIII)

The diagnostic criteria by which a malignant tumor may be recognized on the x-ray film are as follows

1 Visible opacity due to the compactness of the tumor compared with the surrounding tissue. In fatty breasts the growth is usually obvious and very small tumors, even 0.4 cm. in diameter, have been recognized. In younger women with active breasts small carcinomas are difficult to discern, but if even a part of the tumor is showing, diagnosis is possible. In some tumors no definite opacity is visible, but the architecture in the area is jumbled. At first sight the appearance suggests a form of dysplasia, but the pattern is more irregular than in dysplasia and does not conform to any defined type. Surprisingly enough, very large tumors may

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FIG 167 C 554. Advanced carcinoma. Secretory disease. Age fifty-eight years The patient presented a large bulging mass, clinically 7 5×7 5 cm.

A. X ray film shows a large poorly defined mass subjacent to the right areola. In the upper portion of the right breast at least two more poorly defined masses are present. There is disruption of breast architecture. Even in the absence of irregular or spiculated tumor margins, the last finding leads to a diagnosis of malignancy

Left breast secretory disease. Dilated ducts are seen beneath the nipple and extend into the lower quadrant. In this case the diagnosis of carcinoma would be extremely difficult if films of the opposite breast were not also available.

B Slicer section of the right breast shows dilated ducts filled with grumous material. Carcinomatous nodules are seen to the left of them, but growth is nowhere found within the ducts.



FIG 168 C 535 Circumscribed carcinoma (Adenopapillary), showing extensive punctate calcification Age seventy-nine years. Mass in left breast one year.

A. The x-ray film shows a circumscribed nodular mass resembling cysts However the margins are occasionally irregular. The tumor is speckled with innumerable minute calcified particles—usually associated with carcinoma The breast is atrophic

B. Slicer section. The tumor was extremely necrotic Much of it was lost in processing, but outlines of papillary structures can be made out. The skin is thinned out and bulges over the mass.

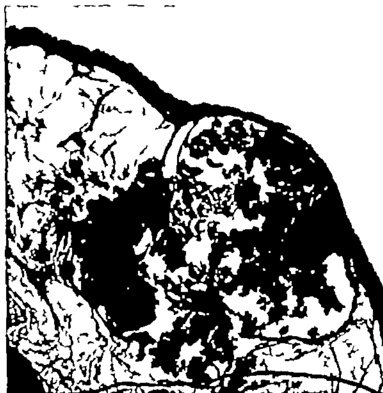


FIG 168
B

infiltrate so widely that they blend with the mammary tissue and differences in density between the growth and its surroundings can no longer be discerned. Opacity is not evident and no margin can be made out. But comparison with the opposite breast at once reveals that none of the structures seen there are present in the tumor area (fig 167)

2. Tumor margin. Spicules and tentacles arising from the growth itself are characteristic of carcinoma. In scirrhous carcinomas they are large and usually very obvious (figs 165, 166) They may extend for long distances They do not follow the pattern of the breast tissue and tend to cut across the line of the trabeculae, an important point in differential diagnosis Some tumors present nodular or even smooth margins It is rare, however, to find a completely smooth carcinoma although such do exist. Most circumscribed carcinomas show at least one area in which strands



Fig 169

issue from the tumor and infiltrate the surrounding tissue (fig 182). They may also show irregularity or fluffiness of one or more borders, in contradistinction to the smooth outlines typical of benign lesions (fig 170)

3 The perifocal zone. Loss of normal architecture in the perifocal zone is characteristic and may clinch the diagnosis when other factors fail (fig 167) It is best determined by comparison with the contralateral organ. Very small growths which are difficult to visualize will often show this feature. Fine reticulation in the perifocal zone can be demonstrated, provided a high degree of resolution is obtained. Nonscreen technic under perfect conditions is necessary, otherwise the reticulation appears as a blur resembling edema instead of fibrosis, which it actually is

4. Comparative clinical and roentgenological size of the mass As pointed out by Leborgne, if the measurements of a palpable tumor exceed the measurements of the tumor on the x-ray film that tumor is malignant. Although rare exceptions to the rule are occasionally found in circumscribed carcinomas, we believe discrepancy of measurement is still a very important sign of malignancy The widest clinical measurement must be taken because the sign depends on induration from congestion, fibrosis, cell infiltration and edema around the tumor, indistinguishable on clinical examination from the tumor itself Comparisons of measurements of tumors on films and in corresponding pathologic specimens show close correlation between the two

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FIG 169 C 362 *Calcification in a mucoid carcinoma Age fifty four years.* The patient presented a large painless mass 5 8 cm. in diameter, immediately beneath the nipple and adherent to it.

A. X ray film shows a well circumscribed mass, except for an irregular posterior margin. Two large flakes of calcium are seen in the tumor together with some smaller particles. Details of the skin and nipple were lost in photographic reproduction.

B Slicer section. The mucoid material in the tumor was lost in processing. This accounts for the honeycombed appearance of its cut surface. The nipple is retracted and adherent to the growth.



A

FIG 170 C 669 Advanced circumscribed carcinoma Calcified fibroadenoma Age sixty years Mass in left axillary tail of several months duration. The overlying skin was raised and reddened and was drawn into a deep sulcus on either side of the tumor The entire breast was edematous and swollen to about twice the size of its fellow The tumor was almost confluent with enlarged axillary nodes

A Films show a well-defined mass (large arrow) Most of the tumor outline is sharply defined, but some irregular infiltration is seen in



FIG 170 A

the upper portion A fold of thickened intracted skin cuts across the tumor (arrow)

Below the main tumor there is a second, partly outlined density (small arrow) containing several coarse calcific deposits. Calcifications of this type may have one of three origins (1) Deposits of calcium in the fibrous tissue of a chronic abscess. (2) Mucoid carcinoma. (3) Calcification in a degenerated fibroadenoma. The third diagnosis was correct.

A Drawing from x ray film.

B. Slicer section of part of the tumor and the fibroadenoma. The tumor is clearly circumscribed by a dense fibrous capsule. The calcified areas are seen as dark patches near the surface of the fibroadenoma. The breast is atrophic and very edematous A portion of fibrosed dermis is seen in the section



FIG. 170. B

5. Calcification. Leborgne in 1951 made the important d
that minute calcified particles could be discerned on the x-
in some 30 per cent of carcinomas. In his book he says. "C
tions are, generally, tiny, dot-like or somewhat elonga
numerable and irregularly grouped very close together in
of the breast, resembling a powdering of fine grains of
description which can hardly be bettered We have ma
confirmed Leborgne's observations and find a similar pr
of typical calcifications, — 29 per cent in our series of
In many specimens the calcifications resemble the br

limit of visibility and in most cases overexposed films are necessary if they are not to be missed (fig 185) The calcified deposits may be visualized within the tumor opacity, but in duct carcinoma, where they are most common, they are often seen in ducts outside the tumor area. Even more common and also pathognomonic for duct carcinoma are focal accumulations lacking polarity, which may be scattered throughout the breast The tumor itself may be quite invisible (fig 192) Later experience has shown that even a few minute calcifications of the type we have been discussing may signal a carcinoma, but some precancerous lesions and carcinomas in situ also show them

Coarser forms of amorphous calcification were met with in 9 per cent of neoplastic tumors, but these are nonspecific and do not betoken carcinoma. The diagnosis of malignancy must be made on other grounds Large flakes of calcium are sometimes seen in long-standing mucoid carcinomas (fig 169) The appearance resembles that of calcified fibroadenoma (fig 170), but other signs of carcinoma are present. In common with Leborgne we have noted scattered calcifications in benign papillomas and in fibrosis The distribution of the calcium is quite different from that in carcinoma. The particles are generally coarser and of different shape and are rarely numerous The calcifications peculiar to secretory disease have been described in the preceding section.

6 Alteration in contour of the mammary gland. Change in contour of the mammary parenchyma as opposed to change in contour of the entire breast can only be detected by comparison with the opposite gland We have noted it in very diffusely infiltrating carcinomas such as lobular carcinomas

Secondary signs of carcinoma are chiefly important because they direct attention to the possibility of a malignant growth. The signs are retraction or deviation of the nipple (fig. 165), thickening, sometimes intraction, of the skin (fig 181), thickening of the fibrous trabeculae in the affected gland, the presence of large tortuous vessels around the tumor, and partial obliteration of the pectoral line.



FIG 171. A



B

Retraction of the nipple is sometimes more obvious on the x-ray film than clinically But before deciding on its significance it is necessary to ascertain whether the condition is unilateral or bilateral. Congenital inversion or retraction, and retraction due to secretory disease, are usually bilateral. Apart from rare cases of involvement of both breasts, retraction in carcinoma is unilateral. Retraction of the nipple due to scar of operation or healed abscess is not likely to be overlooked A cyst or abscess may cause deviation of the nipple. Cysts are easily recognized on the x ray film, but the diagnosis of abscess in a woman past child-bearing age is occasionally a matter of considerable difficulty

Disruption of the pectoral line is seen in tumors near the base of the breast. It is sometimes due to infiltration by the growth, but more often to increased vascularity and alterations in architecture in the perifocal zone.

Before we had mastered the art of mammary roentgenography the presence of thickened skin over the tumor area was an important aid to diagnosis It is always seen over tumors of fairly long duration, even when the growth is at a distance from the skin, but is not present in early tumors Of course it is necessary to position the patient so that the affected skin area is shown in profile. However, with our present technic, this sign has lost its importance Present methods concentrate on showing more clearly the structures within the mammary gland, the skin is apt to be blacked out. The diagnosis of long-standing tumors is usually obvious and it is not necessary to take underexposed films to elicit a secondary sign.

Thickening of fibrous trabeculae, more obvious in the tumor-bearing breast, was sometimes seen on our early imperfect films

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FIG 171 C 12. Advanced carcinoma—vessels in tumor bed. Age thirty seven years. Mass in right breast noted four months Slicer sections

A. The tumor is a circumscribed medullary carcinoma part of which was undergoing mucoid degeneration. The breast shows adenosis and early hyperplastic fibrosis

B Large tortuous vessels in tumor bed.

Better technical methods combined with pathologic studies have enabled a more exact appreciation of the condition, now named hyperplastic fibrosis. Hyperplastic fibrosis is not a sign of carcinoma, but the fibrous hyperplasia is increased in a carcinomatous breast. The part played by hyperplastic fibrosis in tumor-bearing breasts will be discussed later

Increased vascularity is found in the breast in any form of hyperplasia, notably in pregnancy, but never as strikingly as in long-standing carcinoma. Enormous tortuous vessels surround the

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FIG. 172 C 608. Carcinoma Lobular mode of spread. Age thirty-two years. Five months ago patient had pain in the right breast but no mass could be palpated Two months ago there was slight trauma to the breast and patient noted a mass which varied in size, but the variation was not related to the menstrual cycle Three weeks before the operation the surgeon found two masses in the right breast and one in the left breast, but one week before operation there was no mass in the left breast and only one in the right breast. The right breast mass was definitely smaller than when previously examined During this three-week interval the patient had been given testosterone. At the time of operation a tumor 2 cm in diameter could be felt, opposite the marker No definite mass was found in the left breast

A. X-ray film Opacities characteristic of adenosis are scattered through the breast In addition in the lower portion are two small densities with spicules characteristic of scirrhus, see drawing "T." They show disruption of the perifocal tissue Anterior to the lower opacity is a density, "A," caused by a mass of hyperplastic lobules (adenosis) which are undergoing transformation to carcinoma A large vein, V, crosses the upper part of the breast

A′. Drawing of x-ray film, T, tumor; A, adenosis, V, large vein.

B. Tangential slicer section showing parts of both tumors T ... shows that the lower mass is ... lly placed tha The area of adenosis adjace ... tral tumor co "A" on the drawing and was ... ass felt clini sections revealed many isolat ... dergoing mal formation of the epithelial c ... process is a vicinity of the smaller tumo ... ll part of appears ... section.

The sh ... he tumor follo ... e was pr inv ... concomitant ... than to dri ... oma

V

T

A

A FIG 172 A



B

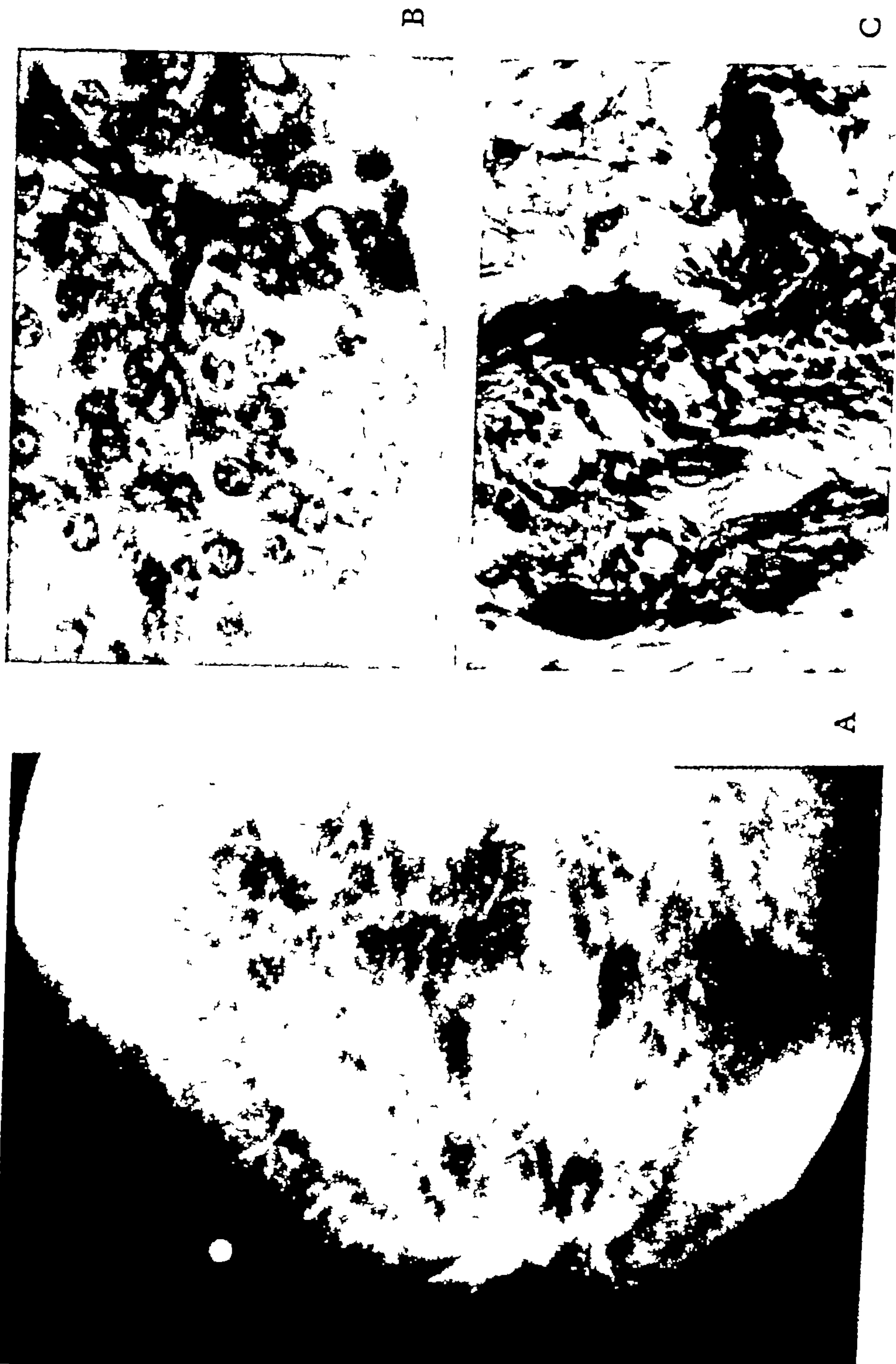


FIG 174

require explanation. Variations in morphology may well be manifestations of mode of spread rather than true differences in the type of cancer. Carcinoma cells grow along the line of least resistance. In soft fatty tissue they spread in all directions. Where the tissue is firmer they tend to travel along clefts between fibrous strands. They may use lymphatics or even blood vessels as a path. They are seen occupying and distending mammary ducts. When no ready-made channels present themselves the tumor compresses the parenchyma instead of infiltrating it and the result is a carcinoma which is almost encapsulated.

Besides growth by multiplication of tumor cells carcinomas also increase by malignant transformation of developing epithelium in their vicinity. The change may take place in lobules or in ducts.

Lobular spread is seen mainly in women in their early thirties with adenosis. Here the carcinoma is often surrounded by an area of hyperplasia (fig. 172). As the cycle proceeds the hyperplastic

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FIG. 174. C 1013. Carcinoma in situ. Age seventy three years. Discharge from right nipple two months, bloody at first, serous later. P.E. No mass felt. Slight retraction of both nipples.

A. X-ray shows irregular opacities above the nipple representing conglomerations of dilated ducts. A number of needlelike calcified particles are seen within the ducts. Some fine punctate calcifications seen in the original x ray film were too small for photographic reproduction. The nipple is retracted.

B. Duct containing carcinoma cells. Pathologic sections showed ducts distended with proliferating cells sometimes papillomatous, sometimes jumbled with abnormal cells among them, as seen in the illustration. No myoepithelium is seen among the tumor cells. One or two elongated cells with fibrillary cytoplasm are seen around a small vessel entering the tumor.

C. Duct at a little distance from the field depicted above. The center is occupied by cells which appear differentiated, but are poorly organized. They show characteristic precancerous proliferation. No myothelial cells are seen amongst them. On the other hand the myothelial cells in the outer part of the wall are extremely hyperplastic; sheaves of cells with fibrillary cytoplasm grow outward into the surrounding tissue. The reaction is a characteristic response to carcinoma in a nearby duct. × 480

FIG 175

A

B

lobular epithelium becomes vulnerable to malignant change. Histologic examination shows tumor cells from the primary growth in the duct leading to a group of lobules During the first half of the cycle the epithelial cells of the ductules appear to grow normally But instead of differentiating as the premenstrual phase approaches, they become larger, lose their polarity, fill the ductule and eventually break through the basement membrane into the surrounding tissue (Ingleby, 1929) (fig 173) This process may occur in a number of foci over a large area. Lobular spread has a dire prognosis Its fullest manifestation is found in carcinomas associated with pregnancy

Malignant transformation of hyperplastic duct epithelium is characteristic of duct or intraductal carcinoma. The tumor extends via ducts and is preceded by intraductal hyperplasia followed by carcinoma in situ before clinical carcinoma supervenes (figs 174,

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FIG 175 C 1232. Carcinoma in situ. Age seventy-seven years. Pain in left breast several weeks On examination the left nipple was considerably retracted. The apex was ulcerated and encrusted. Irregular nodularity was felt above the areola X ray film showed nipple retraction and an opacity above and lateral to the areola.

A. Slicer section shows a deeply retracted nipple covered by a thick amorphous layer, consisting mainly of inspissated shed cells from the ducts and partly of similar material arising from the nipple itself Discharge is present between the folds of thickened areola which enclose the nipple. Beneath the nipple are dilated ducts Many contain inspissated necrotic cells, in some the necrotic material dropped out in processing The wall of the largest duct which arises in the tumor mass is markedly thickened. The tumor was removed separately and only a small part is seen. The breast is fibrous (hyperplastic fibrosis) and shows a remarkable amount of parenchyma for the woman's age. Most of the ducts end in clusters of dilated ductules. The dermis of the areola and of the adjacent skin is extremely fibrotic.

B Paraffin section of the tumor shows dense fibrosis with hyalinization of the walls of the ducts The lumen is filled with lacelike proliferation of undifferentiated cells and partly calcified necrotic material

Clinically the case suggested Paget's disease but no Paget cells were found.

175). Precancerous epithelial proliferation may be adjacent tc tumor or at a distance from it

The above considerations suggest that the pattern of carcinc tous growth might be expected to change from one part of a tu to another, depending on the texture of the mammary tissu process of infiltration In actual fact it does so While the app ance of a tumor is determined in part by other environme factors, e g, those concerned with differentiation and organiza wide differences in one and the same tumor are best explaine the nature of the adjacent tissue

The hypothesis that the gross and histologic appearanc tumors does not reveal their fundamental nature, but stems f the type of breast in which they grow, was tested by indepenc examination of films, pathologic material and clinical data ' specific questions to which answers were sought were: Does type of breast have any bearing on the type of carcinoma or o ability to metastasize? How far does the reaction of the mamm gland to carcinoma influence prognosis? This approach reve the usual procedure and demands a classification of types mammary glands before proceeding to classification of the tum themselves. *It also requires a study of the reaction of mamm* tissue to carcinoma

Normal types of mammary gland were briefly enumerated Part I. The descriptions given there need amplification, abnormal types which have a bearing on carcinoma must be ad to the list. Since the breast is seldom uniform throughout, classification will inevitably show some overlapping, but tak

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FIG 176 C 1292 Advanced bilateral duct carcinoma with transition scirrhus. Age fifty-nine years The patient presented a hard m 3 cm. diameter in the right upper inner quadrant The overlying s was puckered and ulcerated. The tumor was firmly attached to chest wall Other nodules could be felt in both breasts Three ye before, the patient was admitted for cervical polyp A cyst of left breast was excised at this time, but no x-ray examination w made.

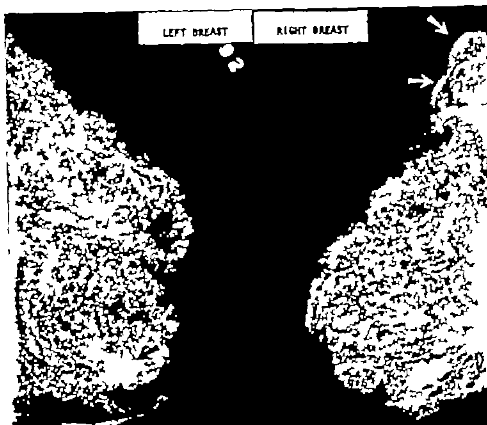


FIG 176 A

Operation—bilateral mastectomy The tumor extended from the skin to the muscle which was infiltrated. Microscopically, ductlike structures and columns of cells separated by dense hyalin formed the greater part of the tumor, but at the edge comedo-like structures typical of duct carcinoma were seen. The metastases were sometimes scirrhous, sometimes typical of duct carcinoma. Slicer sections showed very numerous bizarre lobules in both breasts The distortion appeared to be an effect of the widespread carcinoma. Hyperplastic fibrosis was present in some places Multiple small fibroadenomas were present. They consisted mainly of hyalinized stroma in which were atrophic distorted ducts

A. X-ray films of right and left breast. Both breasts present a number of irregular opacities suggestive of mastopathy with hyperplastic fibrosis. Sparse nonspecific calcifications are scattered throughout the breasts, especially the left. The right breast is smaller than the

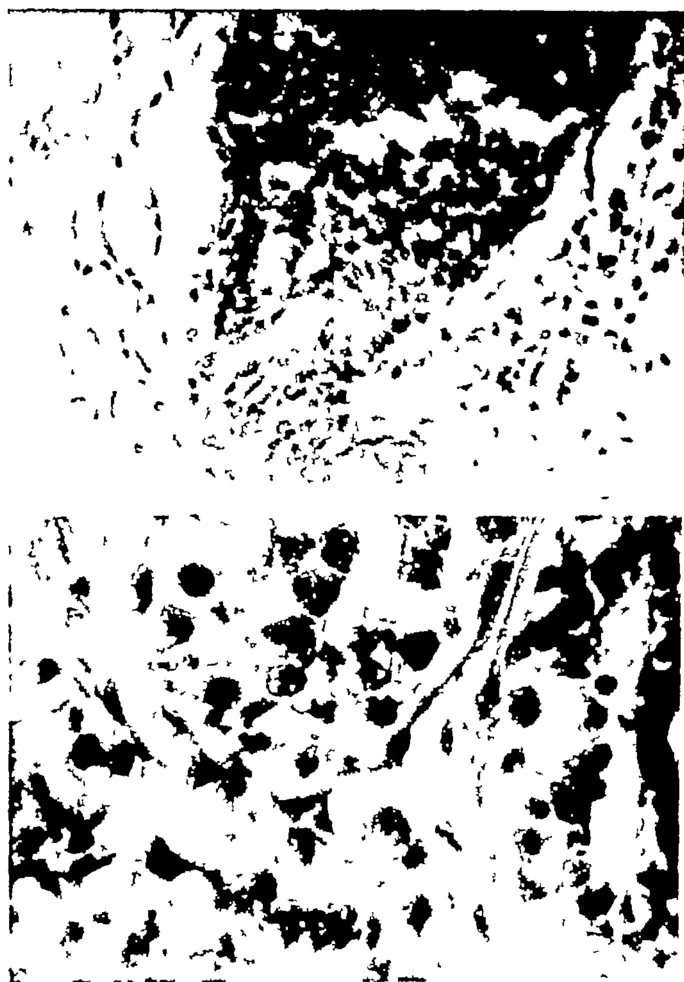


FIG. 176 B

left and contains a carcinoma which infiltrates the skin in the upper part of the picture (arrows) Not all of the tumor is visible due to its proximity to the chest wall. The central arrow points to a cluster of calcifications The lower arrow lies between two veins. In the lower portion of the left breast is a small spiculated mass characteristic of a carcinoma (arrow)

B Left breast Two paraffin sections from the first operation three years before. They show intraductal hyperplasia of the precancerous type.



FIG 176 C

Myothelial cells are scarce. Second section shows cells having almost reached the stage of carcinoma in situ, × 1000 The present operation revealed many similar hyperplastic foci in both breasts. In the left breast a very early carcinoma was discovered near one of them.

C. Right breast. Two slicer sections. One shows nipple with a small metastasis at its apex the second, bizarre lobules and fibrosis Minute metastases are visible, but no details can be made out at this magnification.



FIG. 176 D

D Paraffin section shows calcification of necrotic material in duct

the predominant tissue as a guide, six categories of mammary gland may be recognized Their relationship is expressed in the diagram presented in table III.

Four of the groups are normal, two are pathologic. They are described as follows:

1. The immature breast. The immature breast of adolescence may endure into the early twenties. Prior to the menarche, the mammary gland consists of branching ducts surrounded by fibrous

TABLE III

TYPES OF MAMMARY GLAND

NORMAL		*PATHOLOGICAL*
1. Immature ⟶		2. Immature mazoplastic
3. Glandular - - - →	Adenosis	
4. Involutional fibrous	⟶	6. Hyperplastic fibrous
5. Atrophic		

tissue. Development of lobules begins with the first menstrual period. One or more lobular foci are seen and increase with each subsequent period. Lobules vary in number and are often confined to one part of the breast. The virgin breast of the early twenties seldom shows many lobules They are apt to be more numerous in married women and, as would be expected, they increase greatly as the result of pregnancy The immature gland is predominantly fibrous Except in obese subjects there is little or no fat.

2. The immature mazoplastic breast Not all breasts show the expected lobular structure Some are fibrous with a minimum of lobular development. It is often difficult to say how far these breasts should be considered normal They are usually small. Fibrous tissue makes up the greater part of the gland. There is little or no fat. In the younger women there is close imitation of the adolescent breast, and even beyond the age of thirty years a similar pattern may prevail. However, in abnormal cases certain differences are seen. The intraductal connective tissue is hyperplastic, the lobules are poorly developed and often scanty Sometimes they are numerous, as in fig 177 In many cases the picture is typical of the mazoplasia of Cheatle and Cutler—mazoplasia fibrosa of our classification.

On the x-ray film both types of immature breast are distinguished by an almost homogeneous opacity of the gland. Trabeculae are seldom visible. The only distinction between the adolescent and mazoplastic glands is that in the normal immature breast the surface beneath the subcutaneous fat is smooth, in the mazoplastic breast it is apt to be bosselated.

3 The glandular breast (figs 18, 178) From the late twenties up to the time of the menopause well-developed lobules normally occupy the periphery of the breast. The lobules are not all alike. Some are budding out in response to the menstrual cycle, some are in process of regression. Women in the forties may be expected to exhibit groups of dilated ductules, the counterpart of small follicular cysts in the ovary As the menopause approaches a certain amount of mammary dysplasia is ordinarily found.

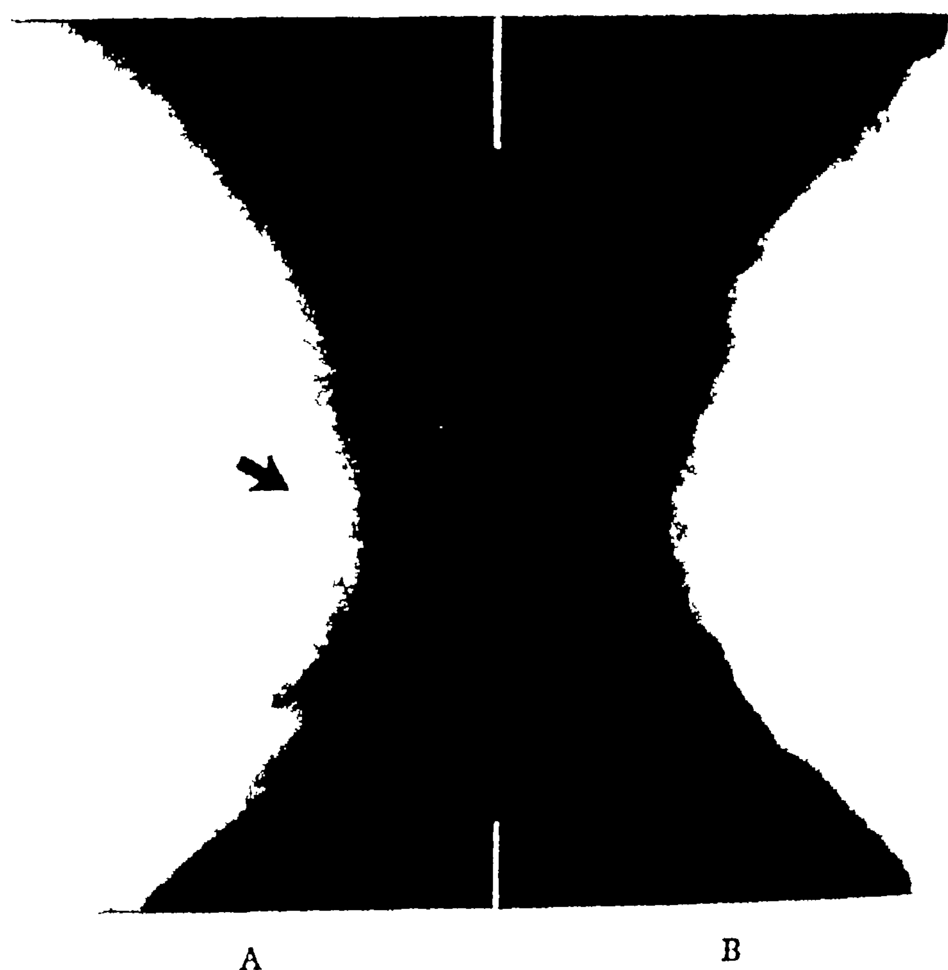


FIG. 177 C 1071. Duct carcinoma Immature breast. Age twenty-two years Slowly growing mass in the left breast noted for three years

A The left breast is larger than the right The nipple is retracted and flush with the surface The tumor (arrows) can be faintly visualized just beneath the nipple Large spicules emerge from it and infiltrate the surrounding tissue The tumor does not stand out from its surroundings due to the density of the breast The skin over the tumor is thickened, the nipple is flattened



A



C

Fig 177

A Drawing of left breast from x ray film. The nipple "n" is shown flush to the thickened skin. The tumor "t" presents broad tentacles

B Right breast. X ray is typical of the immature breast.

C. Slicer specimen. Photo shows part of two slices. The lobules are numerous but poorly developed and are often represented by groups of ducts as in the adolescent. The tumor is spiculated but paraffin sections showed that its mode of spread was that of duct carcinoma.

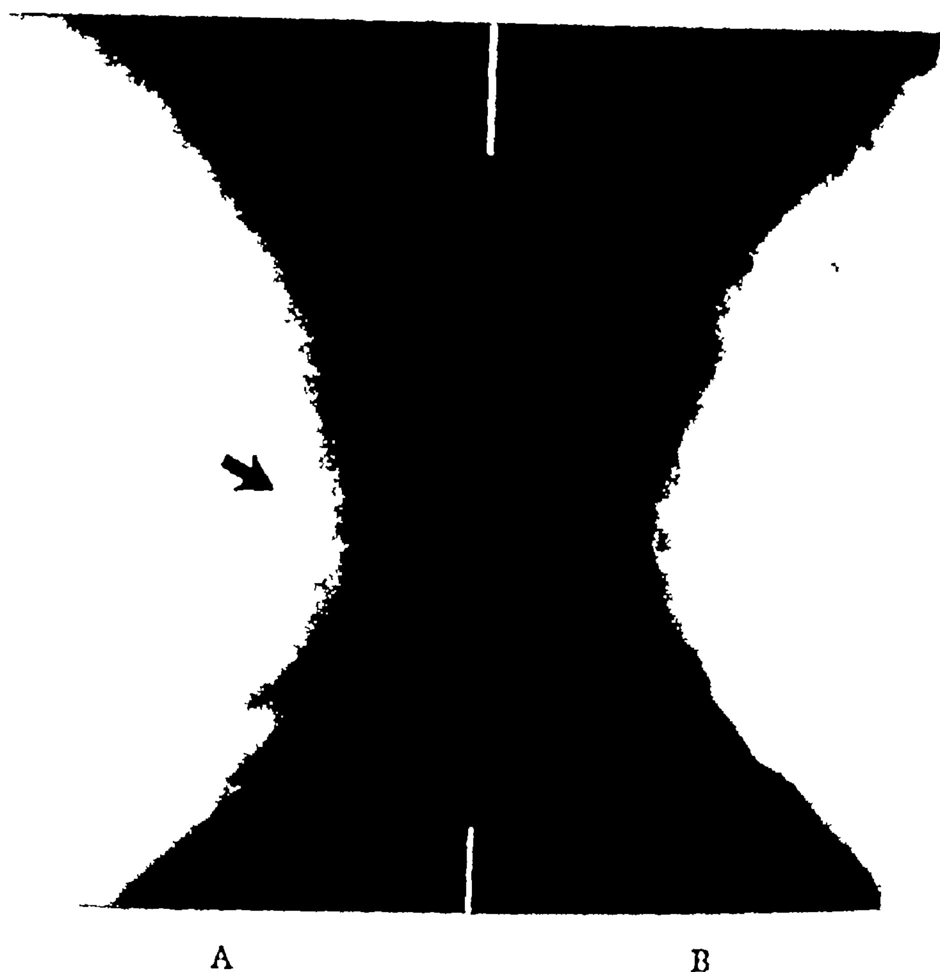


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A



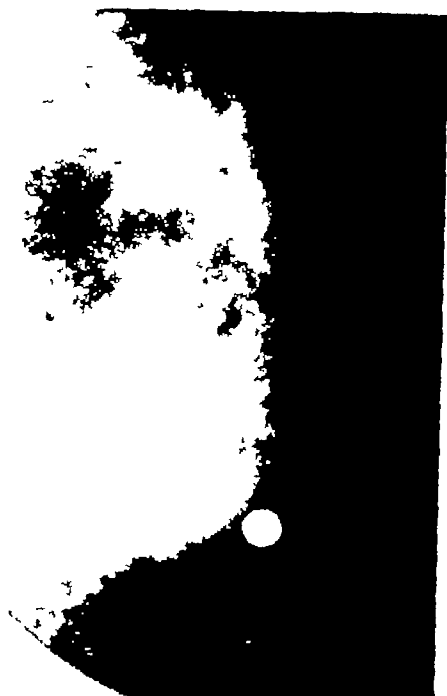
C

FIG 177

A Drawing of left breast from x ray film. The nipple n" is shown flush to the thickened skin. The tumor t' presents broad tentacles

B Right breast. X-ray is typical of the immature breast.

C. Slicer specimen. Photo shows part of two slices The lobules are numerous but poorly developed and are often represented by groups of ducts as in the adolescent. The tumor is spiculated, but paraffin sections showed that its mode of spread was that of duct carcinoma



A



B

178 C 1046 Scirrhous carcinoma Glandular breast. Age fifty-one
ears Menses still regular Mass discovered in the right breast one
month ago.

-ray film of right breast Localized view of the anterior portion of
he breast shows a spiculated mass

eft breast is typical of the glandular type A few densities suggestive
f mild adenosis are seen in it Irregular proliferation is common at
the menopause and could be interpreted as physiologic, rather than
pathologic



C

Fig. 178

C. Slicer section of right breast through the nipple. The tumor was removed at biopsy The lobules occupy their usual position at the periphery those nearest the tumor are hypertrophied. Whether this preceded the carcinoma or was the result of stimulation of the tissue by the tumor cannot be determined. A small fibroadenoma is seen and also portions of a dilated duct running to the nipple



B



A

Fig 179



FIG 179 C 1267 Scirrhous carcinoma. Involutional fibrosis (menopausal) Age fifty three years Retraction of left nipple noted for one year

A. Left breast. X-ray shows a large spiculated opacity in the upper outer quadrant. The nipple is retracted. The breast trabeculae are distorted by the tumor A smaller indistinct opacity beneath the nipple (arrow) represents a second tumor nodule.

B Right breast. X ray shows the fibrous strands typical of involutional fibrosis Indistinct opacities are due to incomplete menopausal involution.

C. Slicer section shows part of a large scirrhous carcinoma in the upper quadrant, secondary tumors are scattered through the breast. The nipple is retracted. A small nodule of growth is visible immediately beneath it. The fibrous trabeculae are distorted.

Typical examples of glandular breasts are most easily studied in women in the thirties In this group the x-ray film of the normal breast with good lobular development, taken in the lateral position, shows fluffy densities at the base and upper part of the breast and to a rather lesser extent in the lower part From these areas fibrous trabeculae, containing ducts and their dependent lobules, emerge more or less clearly and course toward the nipple. As the subareolar region is approached the lobules become fewer and the lactiferous ducts stand out as relatively thin cords The larger ducts can be traced to the fibromuscular pad which underlies the nipple. The tissue here is very dense and the further course of the ducts cannot be followed The normal breast forms a harmonious whole. While there are variations in the degree of development, amount of fat, etc., no interruption of the normal pattern is discerned.

The glandular type of breast is frequently the seat of adenosis, either general or focal, and it is often difficult to draw the line between the normal and the pathologic. For example, circumscribed foci of proliferation are common in adolescents As a rule they disappear as the breast develops, but they may form the nucleus of a fibroadenoma In adults generalized lobular hyperplasia may merely show exaggeration of normal features and would hardly be distinguished from normal breast. On the other hand adenosis is a conspicuous feature of many carcinomatous breasts The objection to classifying adenosis as a separate type is that every gradation is encountered between normal glandular breasts and hyperplastic fibrosis The transition is indicated in table III The effect of adenosis on tumor type is discussed below

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FIG 180 C 1448 Scirrhous carcinoma Atrophic breast. Age fifty nine years Retraction of the right nipple and surrounding skin for ten months.

A. Right breast. X ray shows a characteristic spiculated opacity immediately beneath the nipple. There is marked nipple retraction and thickening of the dermis The breast is atrophic.

B Slicer section. A spiculated tumor lies just beneath the areola. The dermis shows fibrous thickening The breast is atrophic and fatty



B



A

Fig 181

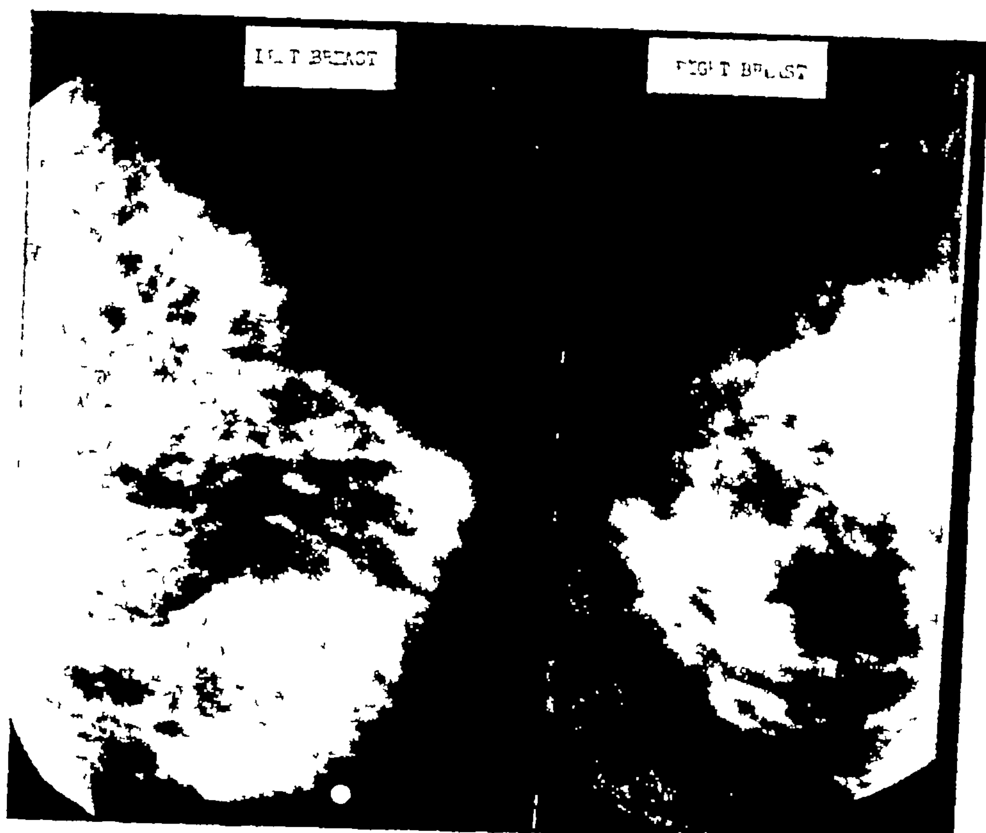


FIG 181 C 387 Scirrhous carcinoma. Intraction of skin. Atrophic breast. Age seventy two years. Mass in left upper outer quadrant noted eight months The overlying skin presented a deep puckered dimple.

A. Left breast. An easily discerned spiculated tumor is present in the upper portion of the breast. It has caused retraction of the skin which is seen as a vertical line (arrow) The breast presents a trabecular pattern.

B Right breast. The trabeculae are thinned out, but lie fairly close together

C. Slicer section. Spiculated tentacled tumor adherent to skin which is markedly intracted. The breast is fatty Trabeculae are not in evidence partly because they are destroyed in the perifocal zone, partly because they do not appear in their entirety in a two-dimensional section.



A

FIG 182 C 459 Circumscribed carcinoma Hyperplastic fibrosis Age forty-nine years Patient presented a large movable mass in the lower outer quadrant of the left breast noted for six months.

A X-ray films. The left breast shows a large rounded opacity in the lower portion The tumor margins are sharply outlined except for the anterior portion A "tail" of tissue extends from the posterior border of the tumor to the pectoral line Clinical measurements of the tumor 6 × 5 cm X-ray measurements 5 5 × 4 5 cm Both breasts show hyperplastic fibrosis In the upper portion of the right breast is a fluffy area representing adenosis

A'. Drawing of left breast; "n," nipple, "t," tail of infiltrating fibrous tissue.

B Slicer section shows a circumscribed tumor except posteriorly where fibrous strands issue from it, and anteriorly where it is adherent to the skin. The microscopic diagnosis was medullary carcinoma.

A



Fig 182.



B



FIG. 182 C

C Ducts under higher magnification show intra- and periductal fibrosis.
Diagnosis of hyperplastic fibrosis is made both from films and sections.

4. The involutional fibrous breast (fig 179) In a glandular breast the larger ducts and many of the lobules are contained in the trabeculae. As the menopause approaches, the epithelial structures atrophy and tend to be replaced by fibrous tissue. After the menopause fibrous tissue predominates. The trabeculae are now actually narrower than when they contained actively functioning parenchyma, and unless they are very close together they are more sharply outlined on the film. Typically, the x-ray film shows a strandlike pattern with bands running from the base of the breast to the nipple Interspersed may be irregular islands of fibrous tissue, possibly the result of involution of a postmenopausal hyperplasia.

The usual tendency is for the trabeculae to become more attenuated as age advances. If adipose tissue is also laid down the

condition merges imperceptibly into the atrophic adipose type. Exceptionally, no fat is found in the breast. The trabeculae lie close together and appear on the film merely as a dense mass

5 The atrophic breast (figs 180, 181) The fatty atrophic breast is characterized by advanced mammary atrophy with extensive fat replacement. It occurs following the menopause whether natural or artificial Atrophy is also seen in endocrine disorders and in cachexia. Ordinarily atrophy is shown by progressive thinning of the fibrous trabeculae. The ducts contained within them shrink and many disappear However, the process is not necessarily regular Foci of duct and even lobular proliferation are frequently met with up to the age of seventy, and even occasionally beyond it In advanced atrophy the x-ray film shows a few thin strands separated by large amounts of translucent fat

6 The hyperplastic fibrous breast (figs 182, 184) Hyperplastic fibrosis is the product of a previous abnormality, usually adenosis The sequence of events has been traced by us in several patients Pathologic sections and x-ray films confirm the existence of stages intermediate between adenosis and hyperplastic fibrosis The change occurs around the time of the menopause and persists into old age. The mammary tissue presents ducts which may be very numerous and are often slightly dilated. They are surrounded by a dense collar of intra- and periductal fibrous tissue. Typically, a certain amount of fat is present between the ducts although this is never excessive. The contrast between the opaque fibrous ducts and the translucent fat gives the characteristic stippled appearance seen on the film and in whole slicer sections Prior to the menopause there may be scanty, poorly developed lobules Later, the ducts end in a clump of fingerlike processes or atrophic lobules are seen which resemble bunches of dead twigs Hyperplastic fibrosis is seen chiefly in the central and upper portions of the breast and varies in extent. Toward the lower margin the ordinary trabeculated pattern prevails Both before and after the menopause the x-ray film shows a stippled pattern likely at times to be confused with adenosis The stippling however is more uniform, the opacities

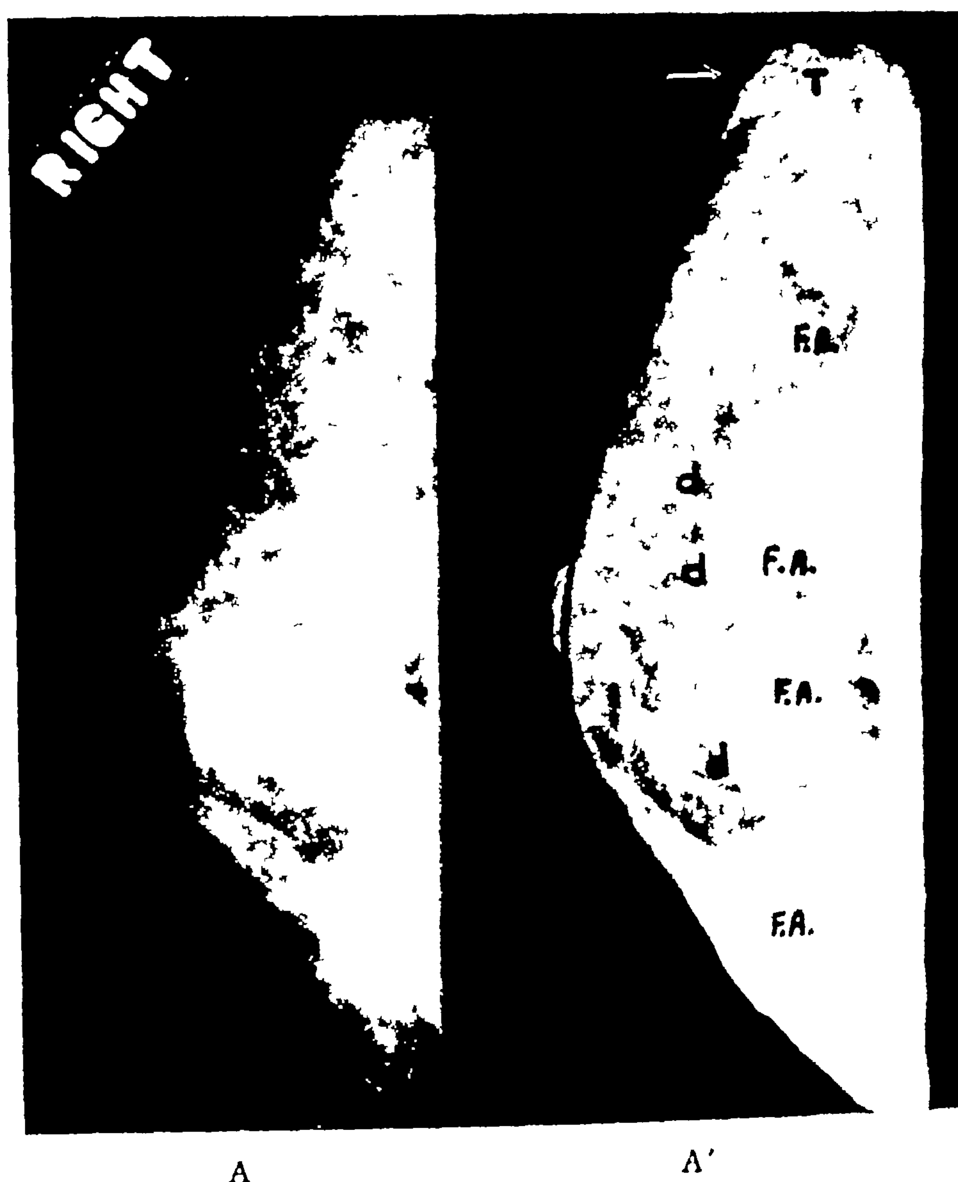


FIG. 183 Duct carcinoma in a breast with adenosis and multiple fibroadenomas Clinically unsuspected. Age forty years The patient complained of a "lump" in the right upper outer quadrant, noted three months previously On examination this was found to be one of several small painless nodules scattered in both breasts. The clinical impression was fibroadenoma

A X-ray film shows a tumor (arrow) less than 1 cm in diameter in the area complained of It contains a cluster of calcific deposits character-

are small, regular, and more sharply defined They may recall ridges left in the sand by the receding tide.

Various forms of dysplasia may of course occur together with carcinoma. They are not types of mammary gland because the manifestations are focal rather than general and do not follow a single pattern. Mazoplasia cystica, for example is varied in its manifestations, there is no sameness in the radiologic or pathologic pattern from case to case Secretory disease produces little or no change in parts of the breast away from the lesion. It is most often seen in otherwise normal breasts The significance of dysplasia in carcinoma is discussed in great detail by Foote and Stewart (1945) Unfortunately for our purpose, they made use of paraffin sections and did not study the entire organ. They have therefore nothing to say on types of mammary gland. Wainwright cut whole sections of the breast in hundreds of cases of carcinoma, but made no classification of breasts in which the tumors grew

In reviewing our films it soon became evident that tumors fell into certain categories, depending on their contour and on the presence and type of calcification seen in and around them. Of 323 cases of the most common tumor types, 89 (28 per cent) had spiculated margins and corresponded pathologically to the so-called scirrhous carcinoma, 109 (34 per cent) were more sharply outlined, circumscribed carcinomas, and were pathologically of the medullary type, 64 (19 per cent) were duct carcinomas and in nearly all cases displayed punctate calcifications either in irregular clusters or following the ducts in linear fashions Sixty-one cases were of mixed type, 20 were circumscribed with a mixture of scirrhus, 41 were duct carcinomas with evolution to scirrhus Six

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istic of duct carcinoma. Elsewhere patches characteristic of adenosis are seen and several opacities which proved to be fibroadenomas. The ducts beneath the nipple are dilated.

A Drawing from x ray film. T tumor F.A. fibroadenomas D ducts.

Pathologic diagnosis Duct carcinoma with transition to scirrhus Adenosis chiefly type A. Fibroadenoma.

(1957) that carcinoma cells in themselves do not as a rule ind fibrosis. They do undergo hyaline degeneration and in some ca extensive hyaline change is responsible for the stony hardnes the tumor. A very important factor, as Jackson and Orr h pointed out, is the broadening of the intraductal connective tis layer and the collagenosis and elastosis within it. The authors not refer to the myothelium, but our observations point stron to myothelial hyperplasia, present to a greater or lesser degre the vicinity of nearly all carcinomas, as the underlying cause of changes in the ducts. Broadening of the intraductal layer is e more obvious in duct carcinoma The authors also state that nip retraction is due to shortening of the ducts rather than to fibrosis around them. Obviously, as Stewart has pointed out, changes responsible for the scirrhous form are degenerative a mostly not of intrinsic origin. They depend on host reaction T original structure of a tumor is of course obscured by the abc changes, but in most so-called scirrhous tumors some arc especially at the periphery, will show characters which differ fr those of the main mass. It is here that evidence of evolution fr another type is likely to be found.

Roentgenographically a scirrhus is characterized by its te tacled and spiculated margin. Although spicules and sometim tentacles are discerned in other types of cancer they are nev as prominent. In a scirrhus the large and numerous projectio catch the eye and make diagnosis easy (figs. 165, 166).

Circumscribed carcinomas (fig. 182) are usually of the so-call medullary variety They commonly show an alveolar arrangeme of large anaplastic cells The stroma is scanty. In some of the tumors glandlike structures are reproduced and the descripti term adenocarcinoma may be used. Stewart rightly objects "adenocarcinoma" in this sense since all breast tumors are glandular origin. In any case, with regard to medullary carcinoma the distinction has no practical importance. Of much greate import is the distinction between medullary and medullary lymphocytic, since here, as Moore and Foote (1949) have showr

the prognosis is relatively favorable. The lymphocytic reaction depends on immunology rather than breast structure. Unfortunately, it cannot be distinguished on the x-ray film Adenopapillary carcinoma (fig 168) deserves recognition because of its slow course, its definite structure and resemblance to a cyst both clinically and roentgenographically Theoretically, confusion could arise between this variety and duct carcinoma in which intraductal papillomatosis is often a prominent feature. Practically, adenopapillary carcinoma is a circumscribed tumor, duct carcinoma is diffuse and widespread Histologically, adenopapillary has a general pattern similar to alveolar carcinoma, papillary areas in duct carcinoma have a lacelike appearance and alternate with the "comedo" pattern.

On the x-ray film circumscribed carcinomas are seen as well-defined opacities, sometimes with smooth margins, resembling those of a fibroadenoma or cyst (figs 168–170, 182) However, careful examination will nearly always reveal at least one irregular border and sometimes a tentacled structure extending into the surrounding tissue. Some circumscribed tumors may show a border of faintly outlined spicules, but spicules are always less pronounced than in the typical scirrhus Discrepancy in clinical and x ray measurements of these tumors is not as striking as in scirrhus, and the sign is occasionally absent. In doubtful cases secondary signs of carcinoma should be looked for The presence of calcification pathognomonic of carcinomas is rare, but would of course clinch the diagnosis (fig 168)

Duct carcinomas* (figs 183–185) spread via ducts and may remain confined to them for long periods of time or even indefinitely (fig 175) In well-established cases, groups of thick-walled ducts containing carcinoma cells are often scattered throughout

*Duct carcinoma is not an entirely satisfactory term since it is also used for tumors reproducing ductlike structures. The alternative, intraduct carcinoma, is unsatisfactory because most carcinomas originate in ducts. It may also be objected that intraduct carcinoma is an apt description of carcinoma in situ The adoption of Leborgne s nomenclature, duct carcinoma saves confusion and is warranted by the importance of his observations.





A A′

FIG. 185 C 311 Advanced duct carcinoma. Age sixty-four years The left breast had felt "a little sore" for nine months, but no mass was noted until eleven days previously On examination an irregular mass about 4×3 cm. was felt medial to the nipple Enlarged nodes were present in both axillae, but only one contained growth

A The x-ray film shows innumerable calcified particles scattered throughout the breast in groups and following the line of the ducts Hyperplastic fibrosis was also present

A′ Drawing from x-ray film to emphasize punctate calcifications

B Slicer sections Nipple area showing hyperplastic fibrosis and a small metastasis beneath the skin near the left margin of the illustration. Two of the slicer sections under higher magnification show the papillary type and the comedo type of duct carcinoma respectively The comedo type presents calcified particles within the ducts



B (1)



Fig 185

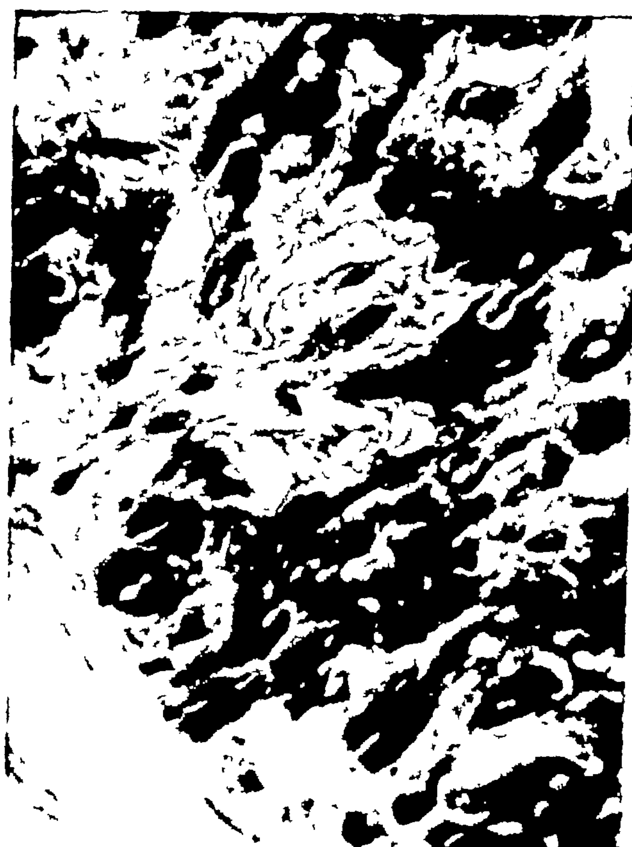
B (2)



B (3)



FIG. 185. C (1)



C (2)

C Two paraffin sections showing invasion of a lobule by cancer cells with destruction of the epi- and myothelial elements and hyalinization of myothelial elements respectively

the breast. A peculiarity of duct cancers is that even extensive tumors may be impossible to recognize clinically for a very long time (fig 192) Sometimes they are nonpalpable, sometimes they are not diagnosed because of other masses On the x-ray film they show clearly as one or more clusters of fine calcifications Near the main mass the calcifications are apt to be linear Until the surrounding tissue is invaded the growth comes under the heading of carcinoma in situ Should there be extensive infiltration the mass takes on a scirrhous conformation, but if the calcium on the film is distributed as described above, the diagnosis of scirrhus superimposed on duct carcinoma can safely be made (fig. 186) A few duct carcinomas do not show calcifications and it may be impossible to distinguish the tumor roentgenographically from other forms Duct carcinomas grow slowly and metastasize late, a tumor of this type may be of large size and still be amenable to surgery, hence the importance of exact diagnosis The relatively favorable prognosis is probably due to marked thickening and hyalinization of the wall of the ducts which is a feature of this type of carcinoma. Paraffin sections show remarkable hyperplasia of myoepithelial cells in the ducts and lobules around and even at a distance from the growth. Fig 192 is an example of the early stage of myothelial hyperplasia in response to duct cancer In this case the response was remarkably widespread. Fig. 174 shows an exceptionally well developed myoid barrier which would account for the tumor remaining in situ for so long

The intermediate forms (fig. 186) are less clear cut and were not listed separately in our first study Before the necessity of making separate categories for these growths was realized most of them were classified as scirrhus In favor of the earlier arrangement it can be argued that scirrhus is really a later manifestation of other types This is largely true, but if development to scirrhus takes place early all trace of the type which preceded it is lost. The prognosis is thereby changed a better knowledge of prognosis is our main objective, therefore the classification which gives the best indication of future prospects is the one to adopt.





A A′

FIG 186 C 1754 Extensive duct carcinoma with superimposed scirrhus in a young woman Age thirty-three years Four weeks previously the patient had a fall when skiing and hit her breast Nothing was noted at the time, but a few days later she felt a nontender mass On examination a conglomeration of movable nodules extended across the breast above the nipple. Near the outer margin the mass turned upward and ended near the axilla The nipple was moderately retracted Examination of the breasts by a physician six months before failed to reveal any pathology.

At operation tumor nodules extended across the breast and ended near a mass of tumor-containing pectoral nodes. The larger tumors were spiculated The breast parenchyma showed extensive adenosis



FIG 186 B

A. X-ray film (tangential view) is characteristic of duct carcinoma. Clusters of calcified particles (arrows) are scattered throughout the breast, but are more marked in the outer portion (arrows). Most of the fine spiculations were lost in photographic reproduction.

A Drawing from an x ray film. "L.N" marks an enlarged pectoral lymph node.

B Slicer section shows several nodules of growth extending from the nipple area across the breast. Tentacles and spicules emerge from the larger masses, but in many places clusters of rounded bodies characteristic of duct carcinoma are seen along their margins and are also present in the intervening tissue. The nipple is retracted.

Of six possible lobular carcinomas, one was an advanced, infiltrating, bilateral growth, grossly and histologically similar to the infiltrating lobular carcinomas described by Foote and Stewart (1946, 1950) (fig 187). No discrete tumor was visible on the x-ray film but the entire mammary gland had lost its characteristic triangular shape. The other cases presented multiple foci originating in lobules. In one, lobular origin seemed certain; the others showed a lobular mode of spread and although it was probable that the tumors were of lobular origin, no certain diagnosis could be made. This group was therefore omitted from the discussion of tumor types. Four inflammatory carcinomas were also omitted

Neither mucoid carcinoma nor Paget's disease are specific entities. Mucoid degeneration may occur in any type of carcinoma. When degeneration is advanced the tumor appears circumscribed and coarse particles of calcium are often seen in it (fig 169). Paget's disease is most often a duct carcinoma arising beneath the nipple (fig. 188).

The results of comparison of 323 breast types versus types of carcinoma are set forth in table IV In ten cases, breast type could not be determined owing to nonspecific fibrosis A glance at the table shows that of 89 scirrhous tumors, 83 (93 per cent) occurred in breasts that were otherwise normal For circumscribed and duct carcinomas the proportions between normal and dysplastic breasts are reversed; combined figures for both types show only 7 per cent with normal breasts. The mixed types occupied an intermediate position.

The definitive adoption of classification based on mammary gland and tumor types must await examination and follow-up of a larger series of cases. Meanwhile the dictum that no classification is of value unless it has clinical as well as radiographic and pathologic application prompted the review of the outcome in 170 cases followed for three years. No final conclusion is possible, but so far as they go, the statistics encourage the belief that the classification is a useful one both with regard to prognosis and as an index of the tumors which are likely to respond to radical treatment. Since

TABLE IV

Distribution of Breast Types in 323 Common Types of Carcinoma

Breast Type

Tumor type	No and Percentage of Cases	Normal		Dysplastic			
		Glandular	Involutional or Atrophic	Immature Mazoplasia	Glandular with Adenosis	Hyperplastic Fibrosis	Nonspecific Fibrosis
Scirrhous	89 (28%)	8	75	1	4	1	0
Circumscribed	109 (34%)	5	6	0	33	60	5
Duct	64 (19%)	0	2	1	29	29	3
Circumscribed scirrhous	20 (6%)	0	4	0	4	11	1
Duct scirrhous	41 (13%)	2	4	1	15	18	1
Total	323 (100%)	15	91	3	85	119	10



FIG 187.

A (1)



A (2)



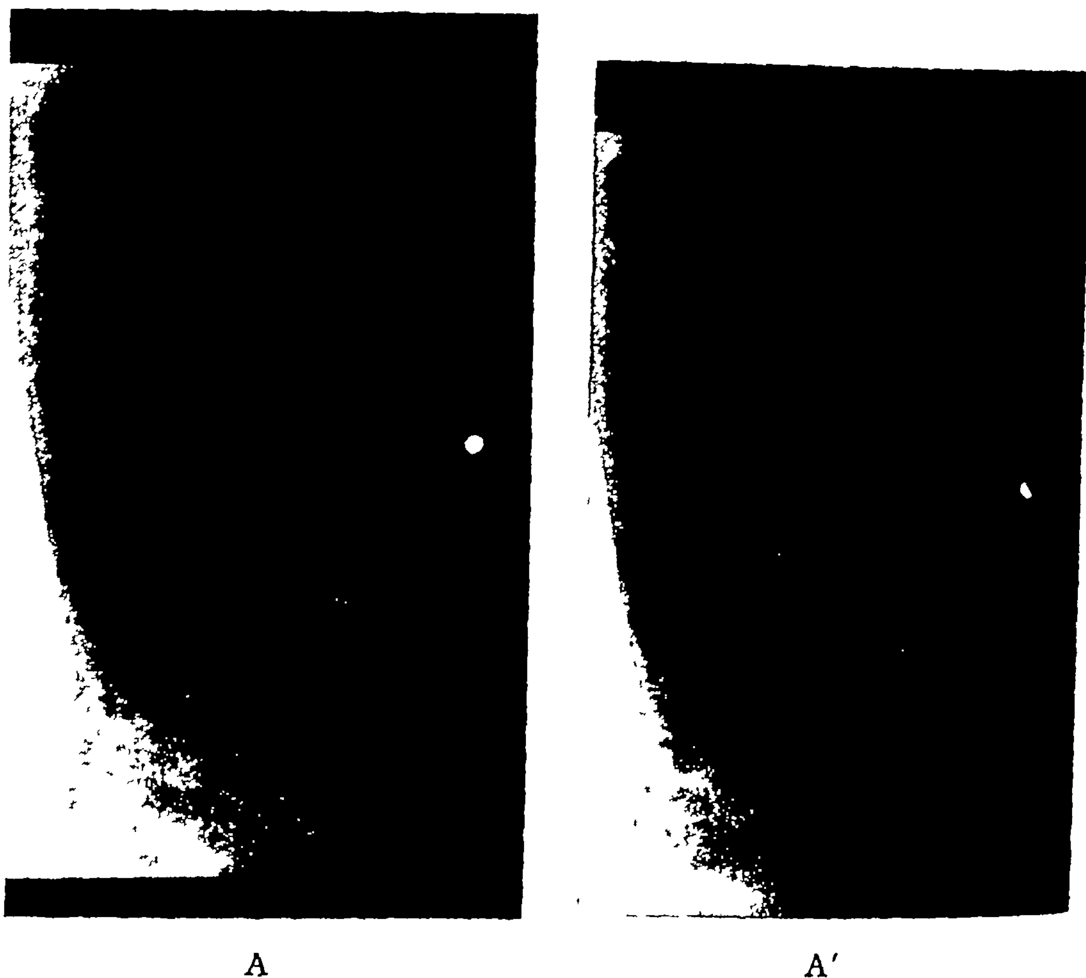
B

FIG 187 C 116 Lobular carcinoma—primary in both breasts. Age forty-six years. On clinical examination both breasts were firm, but no definite mass was palpable. Both nipples were retracted. No tumor was visible on x ray examination or in the gross specimen, but on the x ray film there was complete alteration in the shape of the glands. Instead of a triangular breast, the shape was that of a curved sausage.

Microscopically the entire right breast and most of the left breast were infiltrated with small carcinoma cells separated by dense fibrous tissue. The cells surrounded the ducts, but seldom invaded them.

A. Slicer section through the entire left breast at the level of the nipple shows a large carcinomatous area which looks like normal breast tissue, but was hard on palpation. Small carcinomatous nodules seen as dark points are scattered throughout the breast and in the nipple. A section of the nipple area is magnified about ×4.

B Right breast Paraffin section to show infiltration of tissue by small tumor cells which could be mistaken for lymphocytes in a rapid frozen section. No cancer is seen in the ducts.



A A′

FIG. 188. C 988. Duct carcinoma. Paget's disease of the nipple. Age 69 years. Redness of nipple 2 years. No pain, eczema, nipple discharge, or palpable tumor The left nipple revealed a small cuplike depression Near the outer margin of the areola was a circular, slightly raised serpiginous lesion The surface was characteristic of healed superficial ulcer. Two weeks before operation the nipple was bright crimson. At operation the color had faded.

A The x-ray was taken in the lateral position, but the nipple is not in profile. The depression, seen at an angle, appears ellipsoid rather than cup-like The thickened margins are clearly visible Localized infiltration is present at one end of the ellipse. Calcified deposits, indicating duct carcinoma were seen in this area, but are difficult to recognize in the reproduction.

A′. Drawing of x-ray film.





FIG. 188

B Paraffin section of skin near nipple showing Paget cells.

C. Duct carcinoma beneath the nipple.

Operation revealed a hard mass 4 mm. in diameter attached firmly to the nipple. Slight nodularity was palpable along the line of the ducts A second hard nodule lay beneath the edge of the areola. Sections showed duct carcinoma and typical Paget cells in the epithelium.

there was no opportunity of estimating the duration of these tumors, the best that could be done was to note the outcome in relation to the size of the mass when it was first discovered, and the type of cancer. The result is seen in table V. Out of a total of 47 patients with scirrhous tumors, 28 (59 per cent) are dead; of 68 circumscribed carcinomas, 25 (37 per cent) are dead; of 30 duct carcinomas only 5 (17 per cent) are dead, and of the five, two had cancer spread all through the breast when first seen. The mortality for mixed types, 44 per cent, as might be expected, approaches that of scirrhus.

Many patients with tumors over 5 cm in diameter are in the terminal stage of the disease They are unlikely to live long whatever the original tumor type Therefore no significant differences might be expected in survival times from the group as a whole. However, our figures indicate that whereas the three-year death rate for scirrhus in this group is 100 per cent, for circumscribed cancers it is only 64 per cent This accords with our experience that some circumscribed cancers are of very large size, but give no evidence of metastasis.

In tumors of less than 5 cm. the percentage calculations merely emphasize that the prognostic trend is relatively constant for each type whatever the size of the tumor. It will be noted that the table shows a mortality rate for all scirrhous carcinomas almost double that for circumscribed and duct cancers taken together. The reason for the better prognosis in duct and circumscribed carcinomas is discussed later. Meanwhile enough evidence is on hand to warrant the assertion that the pattern of carcinomas is largely influenced by the type of breast in which they grow, and that rate of growth and ability to metastasize are in all probability conditioned by the same factors.

MAMMARY DYSPLASIA AND CARCINOMA—REACTION OF THE BREAST TO CARCINOMA

The significance of mammary dysplasia in the etiology of carcinoma has given rise to much controversy. A great deal has

TABLE V

THREE YEAR FOLLOW UP OF 170 CANCERS

Tumor	All Types			Scirrhous Cancers			Circumscribed Cancers			Duct Cancers			Mixed Types		
Size	No of Cases	No of Deaths	% Dead	No of Cases	No of Deaths	% Dead	No of Cases	No of Deaths	% Dead	No of Cases	No of Deaths	% Dead	No of Cases	No of Deaths	% Dead
0–1 cm.	15	2	13	4	2	50	3	0	0	6	0	0	2	0	0
1–2 cm.	44	11	25	11	4	36	15	4	27	13	2	15	5	1	20
2–3 cm.	54	17	31	19	9	47	19	5	26	7	0	0	9	3	33
3–4 cm.	22	14	64	4	4	100	11	6	54	2	1	50	5	3	60
4–5 cm.	9	4	44	2	2	100	6	1	16	0	—	—	1	1	100
All tumors under 5 cm.	144	48	33	40	21	52	54	16	29	28	3	11	22	8	37
All tumors over 5 cm.	26	21	80	7	7	100	14	9	64	2	2	100	3	3	100
Totals	170	69	41	47	28	59	68	25	37	30	5	17	25	11	44

been written on the subject, but unfortunately the conclusions drawn by different authors are not often comparable and may even be invalid, either because dysplasias have been treated as a whole and not broken down into separate units or because authors are not agreed on the pathology, classification, and significance of the dysplasias they describe Furthermore there are very few reports which take every aspect of the subject into consideration. Important autopsy studies omit comparison with clinical material; surgical papers make no reference to autopsies.

Exhaustive reviews of the literature will be found in Warren, Kiaer, and others. Such a review is outside our present purpose and we can refer only to the most important conclusions as they affect our own observations.

Shields Warren, in his classical paper, has collected the figures of his predecessors and has given a very careful analysis of the development of breast cancer in 1,206 women operated on for benign dysplasias. He found that the cancer rate for women with preexisting breast lesions was 4.5 times as great as for all women and that it was 11 7 times as great for women under fifty years of age. He could point to no one type of lesion likely to be followed by cancer with the exception of intraductal papilloma. Adenofibroma on the other hand was very rarely associated with cancer. He makes no separate category for epithelial hyperplasia, but he does state that where anaplasia is marked the condition is dangerous. Warren refers to chronic mastitis as an autopsy finding, but no details are given.

Among the more recent contributions to the subject, the monograph by William Kiaer deserves special attention. Kiaer summarizes the work of his predecessors. He then proceeds to analyze in great detail 700 breasts from 350 autopsies and 378 breasts operated on for carcinoma to determine the proportion of "fibroadenomatosis" found in each group. In addition, 321 women who were operated on for fibroadenomatosis were followed for periods up to thirty-five years. Kiaer divides adenomatosis into three grades. Grade I corresponds closely to our adenosis types A and

B and probably also C, but there is no mention of myoepithelial cells so that the proportion of cases which would correspond to type C cannot be determined Grade II is mainly our adenosis D, but the milder benign type of intraductal hyperplasia is also included. Grade III corresponds to our precancerous intraductal hyperplasia and carcinoma in situ. Kiaer's over-all figures show fibroadenomatosis in 33 per cent of autopsy cases as against 60 per cent of carcinomas, but the majority of carcinomas were associated with Grade III fibroadenomatosis No increase in malignancy was noted in Grade I Grade II showed slight increased association with cancer, adenosis D is a purely benign lesion ending in fibrosis, and only the benign type of intraductal hyperplasia was included in this grade. Of the women with clinical fibroadenomatosis, verified by operation, 21 or 6 5 per cent developed cancer Most of them had Grade III fibroadenomatosis

The statistics of Warren and Kiaer are conclusive evidence that mammary dysplasia plays an important part in the genesis of carcinoma and that of the dysplasias, intraductal proliferation is the chief culprit. But we need to go further for a satisfactory solution of the problem. Are any other forms of dysplasia to be considered precancerous? Warren does not give sufficient detail, Kiaer confines himself to fibroadenomatosis In "Comparative Studies of Cancerous versus Non-Cancerous Breasts" Foote and Stewart have described the basic morphologic characteristics of 300 cancer-containing breasts from radical mastectomies and 200 noncancerous breasts from partial mastectomies The paper covers an enormous amount of ground over a wide field and should be read by all who are interested in this subject No summary could do justice to it. We find ourselves in essential agreement with most of the authors conclusions and will discuss them in conjunction with our findings

One method of determining the incidence of mammary dysplasias antecedent to carcinoma as well as the effect of carcinoma on the mammary gland is by study of x-ray films of both breasts This was done for the 323 cancer cases described in the

previous chapter The x-ray diagnosis of the contralateral breast was checked in a few patients by direct pathologic examination of biopsies from the lesion. In other cases reliance was placed on pathologic examination of areas in the carcinomatous breasts which corresponded to the opacities seen in the noncarcinomatous organ. This method of checking is reliable first of all because similar x-ray appearances betoken similar lesions. Secondly, all authors agree that most dysplasias are bilateral. For example, Kiaer notes that severe fibroadenomatosis is always accompanied by a similar milder dysplasia in the opposite breast. We ourselves have noted that adenosis, in many respects similar to the condition reported by Kiaer, is practically always present in both breasts. Thirdly, experience shows that a lesion may elude detection clinically or when only samples of the breast are taken for examination, and yet be demonstrable on the x-ray film.

The cases were tabulated according to whether the patients were above or below fifty years of age, table VI. The line of division is roughly at the menopause but a number of women were undergoing change of life when examined, and corresponding alterations had to be accounted for. Breasts judged physiologic for the menopause were listed under "normal." Examination of 113 women under fifty years of age with carcinoma revealed "normal" breast pattern in only 16, or 14 per cent. Over the age of fifty the number of carcinomas occurring in otherwise normal breasts increases In our series of 210 postmenopausal women over fifty years, 90, or 43 per cent had normal breasts.

Adenosis is the principal lesion discovered on our films of younger women with carcinoma. In 63 per cent it was the chief concomitant disorder. As would be anticipated, in women over fifty years the incidence of adenosis dropped sharply. Adenosis is very common in the general population and is usually associated with premenstrual "tension." It was diagnosed either alone or with other lesions in more than half of the patients under fifty years of age referred to the x-ray department on account of breast symptoms. In earlier days, when x-ray diagnosis was still experimental,

TABLE VI

INCIDENCE OF VARIOUS FORMS OF MAMMARY DYSPLASIAS IN 323 PATIENTS WITH MAMMARY CANCER

Breast Type		Mammary Dysplasias*							
		Mazoplasia Fibrosa	Adenosis	Mazoplasia Cystica	Mastopathy	Hyperplastic Fibrosis	Non specific Fibrosis	Fibroadenoma	Secretory Disease
	50 Years or Over								
Normal	120 (57·1%)	0	0	0	0	0	0	3	22
Dysplastic	90 (42·9%)	1	14	6	8	95	10	19	6
Total	210 (100%)	1 (0·5%)	14 (6·7%)	6 (2·9%)	8 (3·8%)	95 (45·2%)	10 (5·0%)	22 (10·5%)	28 (13·3%)
	Under 50 Years								
Normal	16 (14·2%)	0	0	0	0	0	0	4	0
Dysplastic	97 (85·8%)	2	71	11	15	24	0	11	2
Total	113 (100%)	2 (1·8%)	71 (62·9%)	11 (9·7%)	15 (13·3%)	24 (21·2%)	0	15 (13·3%)	2 (1·8%)
	All Ages								
Normal	106 (32·8%)	0	0	0	0	0	0	7	22
Dysplastic	217 (67·2%)	3	85	17	23	119	10	30	8
Total	323 (100%)	3 (0·9%)	85 (26·3%)	17 (5·2%)	23 (7·1%)	119 (36·9%)	10 (3·9%)	37 (11·4%)	30 (9·3%)

*Figures do not add to total due to overlapping of dysplasias in a number of cases. For example, all cases of mazoplasia cystica or mastopathy were superimposed over adenosis or hyperplastic fibrosis

the majority of cases of adenosis with symptoms came to operation. The diagnosis was thus verified. It is also obvious that the x-ray film uncovers many areas of adenosis that would be passed over clinically. Actually only a minority of cases develop carcinoma, but because in women under fifty carcinoma is usually associated with adenosis, that minority is significant

Hyperplastic fibrosis is a sequel of adenosis and probably also of mazoplasia fibrosa. It appeared in 45 per cent of the older age group. Only 24 of 119 examples of hyperplastic fibrosis were seen in women under fifty years of age. Three had passed the menopause, one had undergone x-ray sterilization, one had a hysterectomy three years before but the ovaries were left intact. The remaining nineteen were still menstruating. Most breasts with hyperplastic fibrosis had either circumscribed, duct or mixed carcinomas (table IV). The only case of hyperplastic fibrosis with scirrhous carcinoma occurred in a woman over fifty years of age.

Mazoplasia of the Cheatle and Cutler type, which we designate as mazoplasia fibrosa, occurred three times with cancer. Cheatle denied any association with carcinoma. We wish we could say the same. Carcinoma in young women in their twenties is rare, but in two out of three cases which came under our observation, the growth occurred in this type of breast. The third patient, a married woman of twenty-one years who had one child, showed a remarkable degree of adenosis. Unfortunately, no x-ray was available in this case

Mazoplasia cystica was present with adenosis or hyperplastic fibrosis in seventeen cases of carcinoma Six of the patients were over fifty years of age, eleven under fifty. Mazoplasia cystica accompanied circumscribed or duct carcinomas sixteen times; it was not found in scirrhus. The unexpectedly high proportion in the over fifty group may be accounted for by the fact that the disease often has its onset in the late forties and the cysts would persist beyond the menopause even if the adenosis had ceased to be active. The relationship of cystic disease to carcinoma has been discussed since the time of Benjamin Brodie. We believe that carcinomas arise in

foci of adenosis rather than in cysts, but since cysts are a sequel of adenosis it seemed important to find out whether breasts with cysts were more likely to contain a carcinoma than breasts in which cysts were absent. Theoretically, large numbers of small cysts indicate a more active proliferation and may be expected to give rise to a larger proportion of tumors Our line of demarcation is perforce an arbitrary one, cysts over 1 5 cm. in diameter are called large, multiple cysts around 0 5 cm to 1 cm., with none larger than 1 5 cm., are classified as small. Both types may advance to mastopathy In cases of mastopathy engrafted on mazoplasia the diagnosis is often a matter of individual judgment on the part of the radiologist or pathologist. Mastopathy was found in 23 cases, or 7 per cent. Eight were over fifty years of age and fifteen under fifty years The distribution was similar to that of mazoplasia cystica. Mazoplasia cystica and mastopathy were never seen apart from either adenosis or hyperplastic fibrosis

In our series of 323 carcinomas, mazoplasia cystica occurred in 17 cases and mastopathy in 23, an over-all incidence of 12 per cent. Foote and Stewart (1945) found cysts in 27 per cent of cancer cases The discrepancy between our figures and theirs is accounted by the fact that they include all cysts 1 mm. or more in diameter, whereas we count as mazoplastic only those which are diagnosable roentgenographically, i.e., 0 5 cm. or more in diameter Cysts smaller than this are usually a feature of adenosis

But before deciding whether and to what extent mazoplasia predisposes to neoplastic disease it is necessary to know the proportion of carcinomas occurring in the course of the disorder In this, Foote and Stewart are unable to help us Their analysis of the findings of different authors leads to the conclusion that 'any point of view one chooses to take concerning the causal relation of so-called chronic cystic mastitis to mammary cancer can be abundantly supported from the literature"—an eloquent testimony to the absolute necessity for proper definition and classification of mammary dysplasia.

In a series of 328 cases of combined mazoplasia cystica and

mastopathy verified by operation, 180 presented large cysts, a few of these were solitary; 148 had multiple small cysts. Carcinoma was present in nine cases with large cysts and in 31 cases with small cysts, an incidence of 5.0 and 20.9 per cent, respectively. From these figures it might be deduced that women with multiple small cysts are more prone to develop cancer than women with large cysts. However, the matter cannot be so easily decided. Unless the small cysts are numerous enough to form a tumor they are unlikely to attract attention. Therefore we have no means of knowing their incidence in the general population.

Malignant tumors arise from undifferentiated cells. It follows that before a neoplasm is formed there must be cells which are capable of proliferation. The origin of carcinoma from simple cysts lined only by a flattened membrane is thereby ruled out. The larger the cyst, the less the likelihood of carcinoma. One would expect a negative correlation between mazoplasia cystica and carcinoma. But mazoplasia cystica is characterized by areas of adenosis from which new cysts arise. It is at this stage, if any, that dangerous developments may occur. When cell division is very active, numbers of small cysts are likely to be formed and the picture is often complicated by intracystic proliferation. It would appear logical to assume that active proliferation is taking place in breasts with small cysts and that there is therefore a greater proneness to carcinoma, but until more information is obtained on the incidence of small and large cysts in the entire population, no statistical proof will be forthcoming.

The x-ray film often does not distinguish between fibroadenomas and cysts, but this is less important than might appear since fibroadenomas are usually the result of adenosis and although they occur frequently in malignant breasts it is rare indeed that they give origin to a carcinoma. In the age group under fifty years, fibroadenoma was diagnosed fifteen times, but was seldom an isolated phenomenon. The tumors were usually part of a more important dysplasia.

Secretory disease was found in only two patients of the younger

group In older women it was present in twenty-eight cases of carcinoma. We believe that this association is fortuitous and the same conclusion was reached by Foote and Stewart in their discussion of "periductal mastitis"—the equivalent of secretory disease with plasma cell mastitis The disorder is very common, some degree of dilatation of lactiferous ducts was present in 8 out of 100 ostensibly normal women and in 97 (6 5 per cent) of 1,500 women x-rayed for breast symptoms In the total series of carcinomatous breasts, the incidence of secretory disease was 9 per cent It would therefore appear to prevail in no greater proportion than in the general population. The carcinomas always arose at a distance from foci of secretion and in spite of careful search, no transition between secretory disease and carcinoma could be discovered.

Although 323 cases analyzed by us are not by themselves enough to be statistically significant, they do afford confirmation of Warren and Kraer's contention that "chronic mastitis" or "fibroadenomatosis" is an important factor in the etiology of carcinoma. When discrepancies in method of approach, nomenclature, etc., are resolved it becomes quite clear that the majority of carcinomas, 86 per cent in our series, under the age of fifty years do so on a basis of mammary dysplasia. The role of dysplasia in carcinomas arising after the menopause is more difficult to evaluate As age advances, more and more carcinomas are found in breasts where no abnormalities can be detected In older women a patch of fibrosis corresponding in location to the tumor was often seen in the contralateral organ (fig 201) From the age of seventy upward most breasts contained scirrhous carcinomas but were otherwise normal. There may be some parallel between the origin of carcinoma in women and in rabbits as described by Greene (1939) In Greene's rabbits carcinomas arose chiefly on a basis of dysplasia with intracystic papillomas But in some animals the growth originated in a duct with no preceding mammary disturbance. In the first group the conditioning factor would seem to be a hormone imbalance with preponderance of estrogens, in the second group

some other cause producing only a focal hyperplasia may come into play. Our experience suggests that some cancers in older women are preceded by a purely focal lesion, but definite proof is lacking.

In the previous section we have discussed the use of the x-ray film in conjunction with slicer sections of the entire breast to evaluate the significance of preexisting bilateral mammary dysplasias on the etiology of carcinoma. It should be added that recent x-ray studies indicate that the incidence of bilateral mammary cancer is considerably higher than the 4 to 8 per cent commonly reported. Indeed we have come to believe that malignancy of the contralateral breast occurs in a large proportion of duct carcinomas. However, growths of this type are so slow that most of the tumors do not reach clinical size within the lifetime of the patient Precancerous lesions and carcinoma in situ are often discovered on x-ray examination of the contralateral breast of cancer patients (fig. 193). Definite conclusions on the incidence of bilateral carcinoma cannot be reached for many years, but in studying the reaction of the breast to carcinoma the possibility that its fellow may also be affected must be kept in mind

Unilateral alterations of structure in a carcinomatous breast may have preceded the carcinoma or may be the result of the growth of the neoplasm. The precancerous lesion most often seen is intraductal hyperplasia already described. In most cases the precancerous pattern will have been replaced by frank carcinoma, but in early tumors the two may be seen together. The hyperplasia, overshadowed by the more important lesion, will hardly be remarked Carcinomas may arise adjacent to scar tissue left by a puerperal abscess many years before. There are also rare cases where carcinoma has followed injection of thorotrast (fig. 189).

Reactive changes in response to tumor growth cause secondary signs of carcinoma seen on the film. Two, namely, increased vascularity (figs. 166, 171), and trabecular thickening, are important. Theoretically, the vascular reaction is an unfortunate one for not only is increased nourishment conveyed to the growth, but tumor cells are carried to other parts of the body.

Generally speaking for any given type the size of the vessels depends on the size of the tumor Enormous vessels are seen in scirrhous tumors of more than 3 cm. in diameter The average survival time for these patients is less than two years

Trabecular thickening secondary to carcinoma is preceded by myoepithelial hyperplasia. Myoid proliferation is observed at a distance from the growth in nearly all breasts with carcinoma. The fact that marked proliferation of myoepithelial cells in the vicinity of a carcinoma is a sign of malignancy, whereas a similar proliferation within a growth is the sign of a benign tumor, may create some confusion. Careful observation of the gross tissue so that the right pieces will be taken for histologic examination, as well as experience in the behaviour of myoepithelial cells, is required for correct diagnosis The Goldner-Masson stain is often of considerable assistance.

The most extensive hyperplasia of the myoid occurs in duct carcinomas (figs 174, 185), and may be seen in the lobules as well as in ducts The process is the same as in hyperplastic fibrosis already described. The hyperplastic myoepithelial cells usually undergo hyaline degeneration, epithelial cells of the lobules may be obliterated and carcinomatous proliferation or infiltration is thereby prevented (fig 185) In the ducts the result is increase in intraductal tissue which may be fibrillary or hyaline. Jackson and Orr (1957) have called attention to the deposit of elastic fibers in this layer Thickening of the walls of the ducts is certainly a factor in the prevention of spread of a carcinoma situated within the lumen. The effect of hyperplastic fibrosis is evidently a slowing down of tumor growth and to some extent prevention of infiltration. Our studies on the comparative rate of growth of cancers show that tumors in a breast with hyperplasia of the intraductal layer grow more slowly than in a breast where the duct walls are not thickened.

Where myoepithelial hyperplasia in involutional fibrosis is an effect of the neoplasm it does not occur in the contralateral breast. Hyperplastic fibrosis following dysplasia, on the contrary, is a

bilateral lesion It may be increased as the result of the tumor, but in itself it is evidence of a preceding dysplasia. On the x-ray film slight thickening of the trabeculae of the carcinomatous breast is frequently discerned. The increase in thickness of intraductal and periductal connective tissue is actually greatest in duct cancers, but on account of preexisting hyperplastic fibrosis is not always obvious on the x-ray film. Thickened trabeculae are apt to stand out more clearly in involutional fibrosis where the carcinomatous breast can be compared with its normal counterpart

DURATION AND RATE OF GROWTH OF MAMMARY CANCER

A carcinoma may be termed "early" because it is small or because it is believed to have existed for only a short time. Both conceptions are extremely vague and serve no useful purpose. The only satisfactory definition of "early" carcinoma is a neoplasm which has not metastasized. Unfortunately, no criterion is available

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FIG 189 C 953 Carcinoma following injection of thorotrast fifteen years previously Age forty-three years. Mass near right nipple of three and a half years duration Fifteen years before, a fibroadenoma was removed from the same area An injection of thorotrast was given before the operation and the outline of the tumor was visualized by x-ray A second similar benign tumor was removed four years later. When the present tumor was discovered the patient refused operation and was treated for two years by monthly injections of testosterone The mass remained stationary The patient discontinued the injections and the mass increased steadily For the last four months there was deviation of the nipple

A The x-ray film shows a spiculated chalky-white opacity just below and behind the nipple which is retracted Pale streaks are continued from the dense area, the site of the original injection of thorotrast, to the posterior part of the breast The thorotrast is just posterior to the carcinoma which is seen only as a thickening under the skin

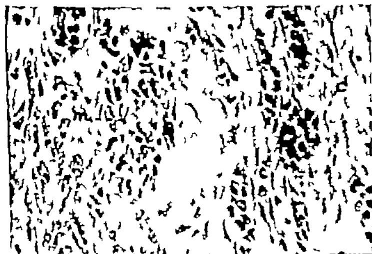
B The paraffin section shows carcinoma (c) and part of the injection material, contained within macrophages (m)

Test for ionizing radiation was markedly positive (10,000 counts per minute recorded by the scaler as against forty per minute background)



A

FIG 189



B

whereby this happy state of affairs can be determined at the of operation. Kreyberg (1953) showed that the tendency to e(earliness with small size of the tumor is not borne out by i Of his group of very small tumors more than two-thirds metastasized when they arrived for treatment. The gene accepted statement that the longer the delay the poorer the r is true only for early cancers, the statistics of Bloom (1950) others notwithstanding. Clinical estimates of duration are no ously fallacious and statistics have so far failed to take the ty tumor into account. Obviously the prognosis of a duct carcin with a duration of ten to twenty years cannot be compared that of a scirrhus which kills the patient in three years. There Kreyberg's observations that where the time lag between appearance of the first symptom and treatment was minimal 50 per cent of patients could count on a five-year survival, incl too many variants to be practically significant. McKinnon (1 in his paper on *The Invalid Evidence for Faith in Early Treat* makes some very pertinent observations He shows that the no real difference between the statistics for treated and untre patients with regard to five-year "cures." In common with I and Lees (1951), Kreyberg, Bloom, Lewison, and others, he monstrates that after three years from the onset of symptoms th is a decrease in the mortality rate for both treated and untrea cases. The authors rightly attribute this apparent discrepancy differences in tumor type and host reaction, but make no atter to define the nature of these differences In the preceding sect we have outlined some factors regarding breast and tumor ty whereby the relative malignancy of a carcinoma may be assessed.

Metastatic growth is the lethal factor in most cases of bre cancer Collins and his associates (1956) in their study of second tumors in the lung showed that the neoplasms in various parts the body from which the lung tumors were derived had nea always metastasized before the discovery of the primary. T authors go so far as to suggest that no palpable tumor is "early Since there is no clear evidence that removal of primary cancer h

any effect on the development of metastases that were present at the time of operation, they conclude that delay in surgical intervention would make no difference to the outcome. In certain cases delay might be of advantage in that a patient may retain a useful organ for some years longer than would otherwise be the case.

The conclusion to be drawn from the perusal of the literature is that not more than 10 to 20 per cent of clinically diagnosable breast tumors are actually 'early' in the sense defined above. Evidently ability to metastasize does not depend on size, and clinical duration has seldom any relation to the real state of affairs But knowledge of true duration of breast carcinomas might give an important clue to prognosis by establishing the rate of growth. It would also allow of a better estimate of the possibility of surgical cure by determining whether there is relation between rate of growth and ability to metastasize.

The first step in the resolution of these imponderables is to determine the average rate of growth of specific tumors For this purpose the only means at our disposal is to calculate the increase in size by measurements of the same tumor taken at suitable intervals Determination of the rate of growth of breast cancers within a reasonable degree of accuracy is impossible by clinical examination. Only palpable tumors can be measured and in nearly all cases clinical measurements depend on the degree of induration of the surrounding tissue and exceed those of the actual tumor by variable amounts Much greater accuracy may be attained by means of roentgenograms The measurements of the tumor as seen on the x-ray film correspond closely to those of the actual specimen. Furthermore, experience has shown that it is possible to visualize a carcinoma on the x-ray film long before it becomes clinically palpable. If, following Collins, a 1 0 cm. nodule is a likely minimal size for clinical diagnosis, the tumor may have already run more than half its life cycle before it is discovered. Knowledge of progress during the first half of tumor life is therefore closed to us without x-rays

In a series of over 400 cases of carcinoma, sixteen had more

than one x-ray study Time intervals between the first and last examinations ranged from five to fifty-one months. In fourteen patients the tumor could not be detected clinically at the time of the first x-ray study In six of these no mass was palpable even at the time of operation seventeen to forty-six months later. In four cases a thickening or a mass was palpable at operation, but thought to be benign by the attending surgeon On the x-ray film all tumors were diagnosed at the last examination. Obviously the discovery of malignancy is promptly followed by surgery or other treatment in nearly all cases. Exceptions are rare One woman, seventy-nine years of age, had a tumor of several years' duration. She refused any form of treatment, but was obliging enough to allow us to take x-rays from time to time (Ingleby and Moore, 1956) (fig. 190). Five tumors 0.2–1 0 cm. in diameter, were missed on the x-ray film due to a lack of experience. In five cases the human element was at fault. One woman had an obvious lesion in the contralateral breast which attracted attention. At operation it was found benign. The x-ray film of the unsuspected breast was not scrutinized with sufficient care and the neoplasm was missed (fig. 191). Three tumors diagnosed by the radiologist were missed at operation. Two carcinomas were encountered which, at that stage of our experience, were undiagnosable when first examined One was a multicentric carcinoma, probably lobular in origin and spreading via isolated lobules. In the early stages the pattern of opacity caused by this tumor was indistinguishable from that of breast tissue and diagnosis could not have been made by the x-ray film alone. Another tumor of lobular origin corresponded to Stewart's infiltrating type and occurred in a woman of forty-seven years Although she had a fatty breast, rather atrophic for her age, there was no palpable mass. The first two examinations at an interval of six months showed an opacity along the line of a large duct, but it was not interpreted as suspicious of malignancy On the third film taken one year after she came to the clinic, the carcinoma was in plain view. Looking back, it was possible to identify the opacity from which

the tumor developed, but even in retrospect nothing diagnostic of carcinoma could be detected at the first examination. The conclusion is reached that not all early tumors are diagnosable even when visible, and only persistent regular examination will bring them to light

The growth rate of these tumors was calculated by tracing their outlines from successive x-ray films onto squared paper The approximate volume was estimated and average rates of growth per month calculated on the basis of an exponential growth pattern The classification of these tumors and the increase in size in each group is set forth in table VII

The determination of growth rate by means of successive x-ray films is open to certain criticisms which can only be met with increasing experience. More data are definitely needed before actual duration can be determined. Collins and his associates were dealing with metastases which grew at a rate which was constant for each tumor as measured by the "doubling time." The authors deliberately chose spherical tumors as affording less chance of extraneous conditions affecting the rate of growth. Constant rate of growth, hence uniform increase in size, would be expected of tumors growing in a relatively homogeneous organ such as the lung. The mammary gland is not homogeneous and a uniform rate of growth cannot be postulated. The fact that breast tumors are seldom spherical is circumstantial evidence that growth is affected by the structure of the organ. The surroundings of a small tumor are apt to be more homogeneous than those of a large one and a more uniform rate of growth might be expected. However, the rate of increase of tumors belonging to the same group did not vary appreciably with the size of the tumor, and tumors that were seen more than twice maintained a fairly constant rate of growth (fig. 202) Should opportunity arise, a comparison of rate of growth of a primary with its metastases would throw light on the effect of host tissue on tumor growth.

Duct carcinomas differ from the other two common forms in that their spread is mainly via multicentric foci arising in duct

epithelium (fig 174). The primary tumor increases very slowly and may remain in the stage of carcinoma in situ even for years (fig. 175) One such carcinoma showed no appreciable increase in size in four months (fig. 193) When the infiltrative stage is reached, the growth outside the ducts is apt to blend with the surrounding tissue and grossly as well as radiologically a definite

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FIG 190 C 1411 Periodic x-ray studies of a growing human mammary cancer Age seventy-eight years The patient had a carcinoma of long duration in the upper outer quadrant of the left breast, but repeatedly refused any form of treatment. Her physican hoped that confirmation of the diagnosis by roentgenography might induce her to change her mind, but this she steadfastly refused to do. However she had no objection to x-ray studies provided we did not press for treatment of the tumor In all, 4 sets of films were taken Twenty-one months after the initial referral the patient entered hospital for repair of a prolapsed uterus At this time she had a mass of axillary and supraclavicular nodes. She was persuaded to have a simple mastectomy done Recovery from these surgical procedures was poor A few months later she died with hemorrhage from a long standing non-malignant duodenal ulcer

A X-rays 1 Roentgenogram on August 18, 1953. A spiculated opacity is seen in the upper portion of the left breast Tortuous, partly calcified vessels surround the tumor The central portion of the nipple is slightly retracted

2. Roentgenogram on July 6, 1954 The tumor shows much the same over-all features as in 1, but is slightly larger. Nodular structures are visible within the mass. The nipple is obviously retracted.

3 Roentgenogram on March 9, 1955 The tumor has grown considerably in size and has extended towards the nipple Large round nodules can be discerned on its surface The tumor outline is smooth at some points

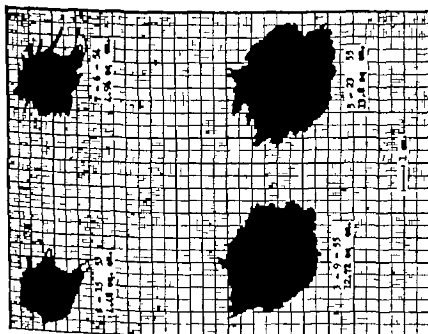
4 Roentgenogram on May 23, 1955. The rounded nodules on the tumor surface have increased in size. The nipple is even further retracted

B. Projection of tumor outlines to illustrate changes in size and rate of growth Tentacles and spicules are not included in the area measurements, since they usually consist of fibrous tissue rather than tumor

C Slicer section of the carcinoma The tumor is mainly circumscribed Beneath the sharp margin an adenopapillary type of growth can be discerned Tentacles and spicules typical of scirrhus issue from one side and merge with the surrounding breast



C



B

FIG 190



A B

FIG 191 Rapidly growing scirrhous carcinoma Age forty-five years. The right breast had a milky discharge from the nipple and near the areola was a small mass which proved benign. No mass was palpable in the left breast. The x-ray films of the contralateral breast were not scrutinized with sufficient care. Five months later the patient returned with a firm mass in the left breast discovered one week before. At operation she had a scirrhous carcinoma. The axillary lymph nodes were free of metastases.

A. X-ray film from first examination An irregularly outlined mass typical of a scirrhous carcinoma is seen

B X-ray film from second examination The 's considerably larger and more spiculated Scattered c ied particles are seen on both oc . They are the sc tory disease and are not relate cinoma.

C Tracings of tu n successive have been superimposed



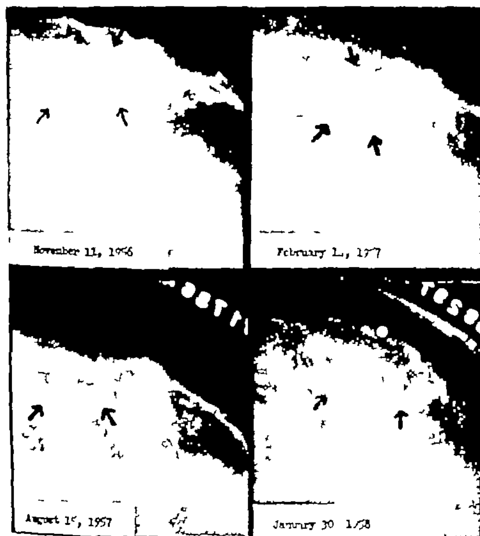
FIG 191 C

boundary may not be seen. The clusters of calcified particles point out the site of tumor nodules, but the growth itself cannot be measured. For example, in a case engrafted on mazoplasia cystica the film showed secondary very small carcinomatous foci widespread through the breast. They were scarcely more than a millimeter in diameter and no distinct boundaries could be seen Another case in which the surgeon refused to operate because he could find no tumor was observed by us over a period of fifteen months The growth could not be measured, but the spread of the disease was followed roentgenographically by the appearance of tiny calcifications in areas where they were not previously visible. The carcinoma was still not palpable when the surgeon finally acceded to the family's request that an exploratory operation be

TABLE VII

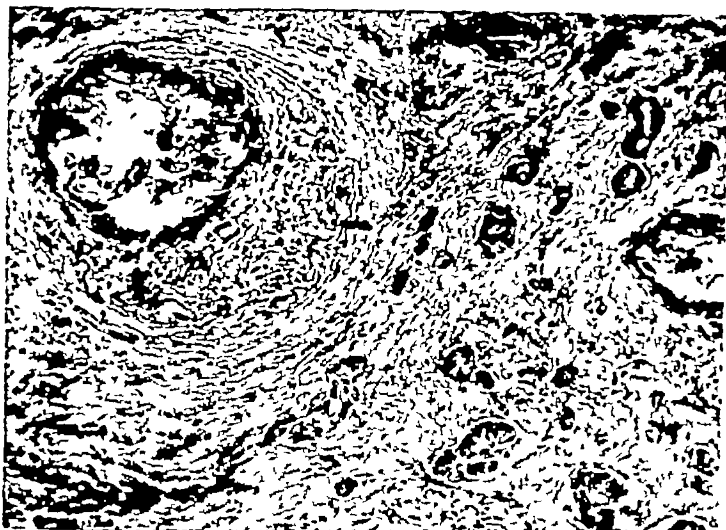
Observed Growth in 16 Mammary Cancers

Res. No.	Type of Carcinoma	Age*	Tumor Volume		Average Tumor Diameter		Time	Rate of Growth
			First exam	Last exam	First exam.	Last exam	(in months)	(per month)
C 1189	Duct	45	0 19 cm^3	0 97 $cm.^3$	0 72 cm.	1 22 cm	46 6	1 03
N 341	Duct(5)**	45	0 38 cm^3	0·59 $cm.^3$	0 90 cm.	1 17 cm	19 0	1 04
C 2617	Mixed (duct-scirrhous)	70	0 91 cm^3	4 19 $cm.^3$	1 20 cm	2 00 cm.	51 0	1 04
C 1740	Duct	37	0 19 cm^3	1 27 cm^3	0 72 cm.	1 34 cm.	37 5	1 05
N 194	Circumscribed	41	0 75 cm^3	1·12 cm^3	1 14 cm.	1 29 cm	7 0	1 05
C 1195	Circumscribed (Papillary)	78	0 35 cm^3	0 97 cm^3	0 86 cm	1 22 cm.	21 3	1 05
N 355	Duct(5)	45	0 61 $cm.^3$	2·20 cm^3	1 06 cm	1 61 cm.	22 6	1 06
C 2795	Circumscribed(4)	33	0 11 $cm.^3$	0 55 $cm.^3$	0 59 cm.	1 02 cm.	22 0	1 07
C 2838	Duct	47	0 03 cm^3	0 48 cm^3	0 38 cm.	0 97 cm	37 3	1 08
N 629	Duct(4)	75	0 41 $cm.^3$	1 63 $cm.^3$	0 92 cm.	1 46 cm	17 6	1 08
N 881	Infiltrating Lobular(3)	47	0 79 cm^3	2 31 cm^3	1 15 cm.	1 64 cm	12 6	1 08
C 1411	Circumscribed (Papillary)	79	9 49 $cm.^3$	50 99 $cm.^3$	2 62 cm	4 59 cm.	21 5	1 08
N 1037	Scirrhous(4)	66	0 90 cm^3	4 19 cm^3	1 20 cm	2 00 cm	11 3	1 15
N 221	Probable Lobular(3)	43	0 07 $cm.^3$	0 56 cm^3	0 51 cm	1 02 cm.	12 3	1 18
N 1224	Scirrhous	54	2 07 cm^3	6 20 cm^3	1 58 cm.	2 28 cm	6 0	1 20
C 1407	Scirrhous	45	3 15 $cm.^3$	12·15 $cm.^3$	1 82 cm.	2 85 cm.	5 3	1 29



A

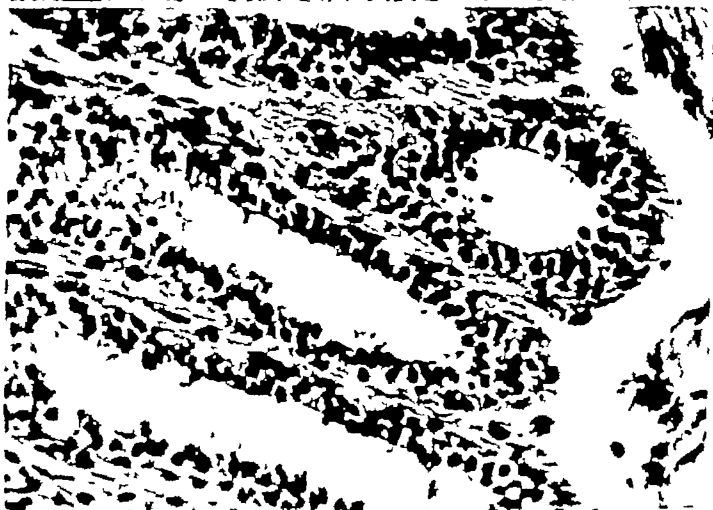
FIG 192. N 971 Unsuspected duct carcinoma. No palpable tumor Age fifty four years, married, had no breast symptoms Premenstrual pain was complained of at one time, but had ceased at the menopause two years before. Clinical examination revealed lumpy breasts but no specific mass The x ray films showed bilateral adenosis In addition the medial edge of the left breast presented very extensive punctate calcification. The diagnosis was duct carcinoma. The case was referred to an experienced surgeon who examined her monthly for fifteen months but refused to operate because he could distinguish



B 1.



B 2.



B 3.

FIG. 192

An infiltrating duct carcinoma 3 mm. in diameter was
ered Microscopic examination revealed widespread pre-
ous intraductal hyperplasia with extensive calcification of
erated epithelial cells (fig 192)

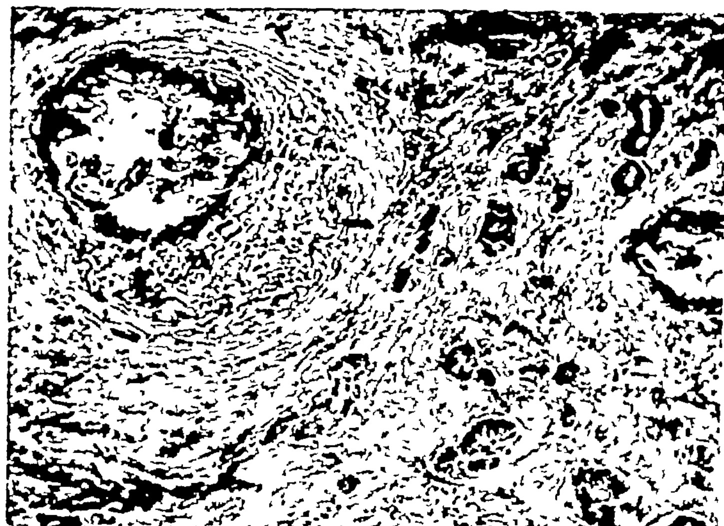
irt from the difficulties of measuring them, duct carcinomas
problem when it comes to estimating duration It is quite
le for the primary focus to remain stationary for long
s, but secondary foci may be in a state of active proliferation
ossibility of multiple primary foci must also be allowed for
t carcinoma which remains true to type may be localized to

92 (continued)

nass suspicious of carcinoma. During this time the area of calci
tion had extended but the tumor was still not palpable. Explora-
7 operation was undertaken at the insistence of the radiologist.

ay films taken at intervals of three, six and five months, respec-
ly The x ray film shows scattered punctate calcifications patho-
monic of duct carcinoma (arrows) Their number increased
dually On the last examination a marker was placed on the skin
rder to localize the tumor for the surgeon Unfortunately, in the
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nor Lack of cohesion of the epithelial cells noted by Stewart in
ly cancers is seen here. This together with focal change in
arity suggests that carcinoma in situ is the more appropriate
ignation for the lesion.



B.1



B 2



B 3

FIG. 102

done. An infiltrating duct carcinoma 3 mm. in diameter was discovered Microscopic examination revealed widespread precancerous intraductal hyperplasia with extensive calcification of degenerated epithelial cells (fig 192)

Apart from the difficulties of measuring them, duct carcinomas pose a problem when it comes to estimating duration It is quite possible for the primary focus to remain stationary for long periods, but secondary foci may be in a state of active proliferation. The possibility of multiple primary foci must also be allowed for A duct carcinoma which remains true to type may be localized to

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FIG 192 (continued)

no mass suspicious of carcinoma During this time the area of calcification had extended but the tumor was still not palpable. Exploratory operation was undertaken at the insistence of the radiologist.

A. X-ray films taken at intervals of three, six and five months, respectively The x ray film shows scattered punctate calcifications pathognomonic of duct carcinoma (arrows) Their number increased gradually On the last examination a marker was placed on the skin in order to localize the tumor for the surgeon Unfortunately, in the reproduction most of the smaller, more recent calcifications do not appear

B. Paraffin sections (B 1) Shows scattered clumps of carcinoma cells, sometimes with indication of a central lumen Two ducts contain partly calcified carcinomatous debris The larger duct presents a semilunar thickening in the subepithelial layer containing fine fibrils and coarse hyaline strands together with a few carcinoma cells and lymphocytes 142× (B 2) Two ducts with cribriform carcinoma and calcification of necrotic cells In the smaller duct the calcium particles are minute and include only a few degenerated cells. But these cells as elsewhere in the section and in other duct carcinomas are invariably detached from the surrounding living epithelial elements (*cf* fig 194) The remains of another duct represented by a hyalinized crescent and a lumen filled by a meshwork of fibrillary tissue is seen between the carcinomatous ducts. We agree with Muir and Aitkenhead (1934) that this could be a process of healing. 142× (B 3) Precancerous epithelial hyperplasia with myothelial hyperplasia in the breast at some distance from the tumor Lack of cohesion of the epithelial cells noted by Stewart in early cancers is seen here. This together with focal change in polarity suggests that carcinoma in situ is the more appropriate designation for the lesion



FIG. 193 Carcinoma in situ Age forty-five years The patient was first seen for multiple masses in both breasts In the left breast the x-ray films revealed a small irregular mass, clinically masked by numerous small cysts At operation this proved to be a mucoid carcinoma and left radical mastectomy was done

A X-ray films of the right breast disclosed an area in the upper outer quadrant with minute punctate calcified particles The tumor was partly surrounded by a clear zone, but its posterior border was slightly irregular Mazoplasia was confirmed by biopsy, but the suspicious area seen on the x-ray film was not excised

B Four months later the tumor showed no apparent increase in size However, there was an increase in the number of calcifications seen within the lesion. The area was now removed Pathologic diagnosis was carcinoma in situ

the breast for ten years or longer The contralateral breast may be affected, but this could well be a second primary The prognosis becomes considerably worse when the duct carcinoma goes over into the scirrhous type. Its behavior is then that of a scirrhus (fig 186).

Measurements based on the rate of increase of growths of multicentric origin or of multicentric lobular spread cannot be accepted at their face value. Foulds demonstrates multiple cancers in hyperplastic foci in mice which eventually coalesce to form a large tumor The same thing happens in human breasts On the film it may be impossible to tell whether the tumor arose simultaneously at multiple points or whether a single primary cancer gave origin to others by a lobular mode of spread. In either case a sudden increase in size might be due to coalescence of growths too small to have been located on previous examinations We have measurements of one case, N 221 in table VII, apparently of lobular origin, with minute foci in lobules scattered over a wide segment of the breast. Three examinations were made at six-month intervals and equal increments were noted. The tumor was nonpalpable and measured only 0 2 $cm.^2$ at the first examination The growth rate was nearly that of a scirrhus, but had it been allowed to continue its development it is possible that a sudden large increase would have been noted. However, in a case of this kind, even if coalescence of tumor nodules could not be deduced from the x-ray films, the anatomic specimen would give a clue to the anomalous measurement.

The possibility of tumor regression has to be kept in mind Unless a very careful appraisal of the situation is possible, results of measurements could be extremely misleading Examination of certain cases of recurrent tumors suggests the possibility that carcinoma arising during the active stage of adenosis may not declare itself for many years A clear history of carcinoma arising on the basis of a tumor that had disappeared months or even years before was elicited in four out of 250 cases of cancer The following is a summary of the case histories

C 263. The patient, aged thirty-four years, complained of two masses in the right breast. They were first observed one year before, following a blow which rendered her unconscious. No clear history of injury to the breast was obtained. The tumors described as "the size of a pea" disappeared two days later. Two months previous to the x-ray examination the nodules reappeared and persisted The breasts were painful for two weeks before the menses and the tumors were said to increase in size during the periods. On examination, firm, freely movable, nodular masses, tender to touch were found at 5 and 7 o'clock. The x-ray film revealed one carcinoma; the other tumor, of microscopic dimensions, was not visible. Adenosis was present in both breasts. At operation a biopsy was made of both nodules. One of them revealed a spiculated tumor 1.5 cm. in diameter. No tumor could be found grossly in the other, but duct carcinoma and one small scirrhous nodule were discovered microscopically Duct carcinoma was also found at the periphery of the spiculated "scirrhous" carcinoma in the first piece examined There were no lymph node metastases The patient has remained well for five years. The left breast has been reexamined at intervals. When last seen adenosis was still present.

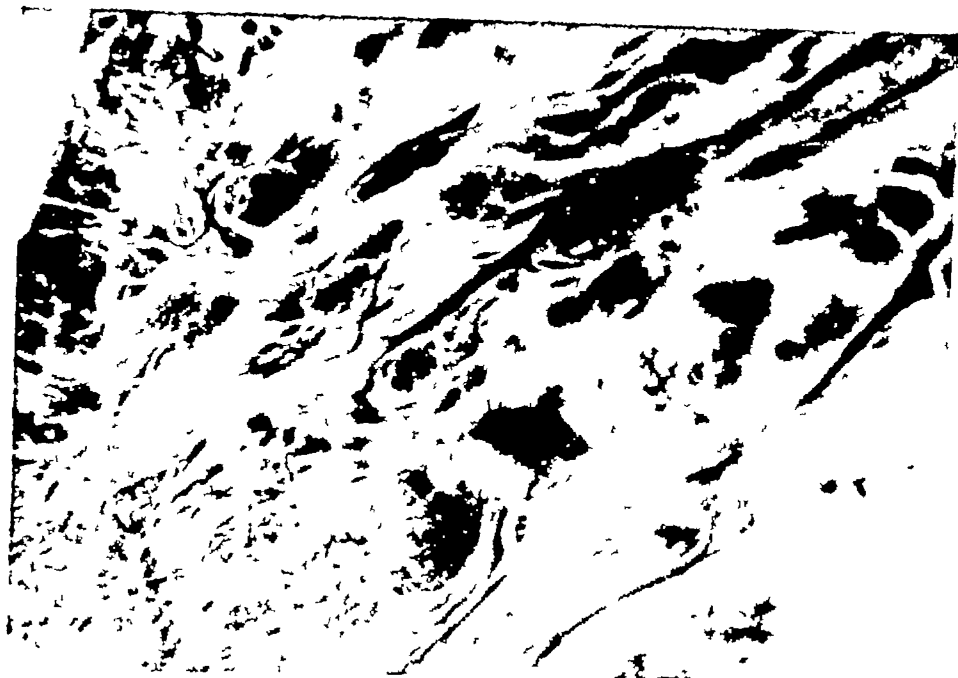
C 608. The patient, aged thirty-two years, complained of pain in the right breast seven months before admission to hospital, but no mass could be felt at that time. Two months ago there was slight trauma to the breast and the patient noted a mass which varied in size, but the variation was not related to the menstrual cycle. Five weeks before operation she received injections of testosterone twice weekly. Three weeks before operation she was seen by a surgeon who found two tumors in the right breast and one in the left breast One week before operation there was only one mass in the right breast and none in the left. The tumor in the right breast was definitely smaller. The x-ray film (fig. 172A) showed a spiculated opacity difficult to distinguish from an area of adenosis At operation a carcinoma about 1 cm. in diameter was found in that area Microscopically the growth consisted of ductlike structure-

Beyond the main mass were large lobules, some of which were carcinomatous, others merely hyperplastic. Study revealed extension of the growth by transformation of lobules into carcinomatous areas Slicer sections showed two small spiculated carcinomatous nodules connected by a thin strand Lobular invasion by the tumor could be clearly made out. The axillary nodes contained small metastases

C 370 The patient, aged sixty-six years, noted a mass in the right breast three years previously It disappeared a month and a half later The present tumor at the same site was found seven months before the x-ray examination which revealed a mass 5 cm. in diameter lateral to the areola, attached to the skin. Both breasts were dense and fibrous, so much so that a biopsy was taken to exclude tumor in the left breast. Microscopically the carcinoma was of the circumscribed alveolar type. The breast tissue contained numerous slightly dilated ducts and atrophic lobules, the aftermath of an extensive adenosis The lumen of the ducts was surrounded by a broad collar of fibrous tissue (hyperplastic fibrosis) A similar condition was present in the left breast. The patient did well, but died suddenly two years later from a cerebral accident.

C 1516 Age fifty years Six years ago the patient noted a mass in the left breast following a course of hormone therapy for menopausal symptoms The tumor disappeared spontaneously Three weeks prior to the x-ray examination a mass was noted in the same location. A scirrhous tumor, 1 8 cm. diameter, was attached to the skin. X-rays showed a dense fibrous breast.

Malignant progression in recurrent tumors has been described by Foulds (1949, 1954) in mammary glands of mice and the cases recorded above are evidence that a similar progression may occur in women Women and mice were alike in that there was no constant time interval between the disappearance of a tumor, its recurrences, and its malignant manifestations The mouse tumors were hormone responsive They grew during pregnancy Some increased progressively, but some regressed partially or completely after parturition After a longer or shorter time, hormone respon-



A

FIG. 194. C 173 Adenosis. Marked intraductal hyperplasia with calcification. Age 49 years. Freely movable mass 3×2 cm. noted one week. Operation specimen revealed a few small cysts and one compact glandular area

A Slicer section away from the tumor shows adenosis A and B with occasional formations characteristic of type D.

B 1 and 2 Paraffin sections from the circumscribed nodule. The epithelial cells are extremely hyperplastic They vary considerably in size; the majority are larger than normal Degeneration of individual cells and of small cell groups is a prominent feature. Calcification is common (2 "c"); it may be confined to one cell or form part of a fused cell complex. Clumps of degenerated cells are found more often in the wall of the ductules than in the lumen A peculiar feature and one not often encountered in our experience, is the presence in many places of a calcified cell or cells surrounded by functional epithelium The myoepithelium is markedly hyperplastic, but the cells are regular and their development follows the pattern common to benign hyperplasias 1 "d" is an intralobular duct covered by a dense myothelial layer. In 2 hyalinization of hypertrophied fibers has begun

FIG 194. B1

B2

siveness was lost and the tumors continued to grow. The time factor for loss of responsiveness was extremely variable. It might exceed the life span of one animal and the change might be observed only after grafting into a second host. The changes in Foulds' mouse plaques during regression following pregnancy are certainly akin to those of human adenosis In some mice minute foci of carcinoma were detected in the degenerating areas. One suspects that the malignant cells survive the general destruction of the epithelium in the plaque and are the nucleus for the subsequent neoplasm A similar focus in humans would be far too small as a rule to be detected clinically and would have little chance of being included in a histologic section. Figure 194, the only case of its kind we have encountered, illustrates a possible precancerous lesion arising in an area of adenosis. If a plaque of adenosis in a woman is going to be the site of a carcinoma, measurement of the

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FIG. 194 (continued).

The interest in this case lies in the sharp contrast in behavior of epithelium and myoid As regards epithelium the question of malignancy is raised by the irregularity of the epithelial cells, the large size of many of them and the calcification of degenerated elements. But the regular formation of myothelial cells is not to be expected in the tumor area of a fully developed carcinoma and the diagnosis of cancer could therefore be accepted only with the greatest reservation. The state of affairs is comparable to that seen in *fig 174, p 334*, where precancerous epithelium is surrounded by hyperplastic myothelial cells. In duct cancers it is usual to see fairly large clumps of degenerated cells which then become calcified. Here the process is taking place in a lobule. Single cells or clumps of two or three undergo calcification and the adjacent cells retain their vitality It could be that the vigorous myothelial reaction is due to the greater functional response of lobular as against ductal tissue. In the case under consideration it is perhaps reasonable to regard the lesion as precancerous and the myoid proliferation might well have been successful in preventing the development of clinical carcinoma of the lobular type It is tempting to speculate that prompt and effective laying down of a myoid barrier is the reason for the comparative rarity of lobular carcinoma But without more experience and study of this type of lesion no conclusions can be drawn

plaque might be mistaken for that of the neoplasm itself and a completely false idea of the rate of growth obtained

Lobular hyperplasia initiated by pregnancy anteceded tumor formation in the mice, lobular hyperplasia (adenosis) preceded carcinoma in the first two women with recurrent tumors and probably did so in the last two Case 370 which was adequately studied gave clear evidence of adenosis which had preceded the fibrosis In view of the very long latent period which may intervene between the disappearance of a tumor and its return with progression to malignancy, it is fair to assume that the tumors under consideration originated many years before, during the florid phase of adenosis The tumor sparked by the administration of estrogens was probably a recurrence. The part played by hormone medication in the genesis of this carcinoma can only be a matter for speculation, but the case history should serve as an additional warning of the inadvisability of prescribing estrogens in cases of adenosis

Although investigation of tumor duration is still in its infancy two points are clear (1) The average rate of growth of scirrhous carcinomas greatly exceeds that of circumscribed and duct varieties. The excess is well outside the margin of error and confirms previous observations that patients with scirrhus succumb to the disease earlier than those with circumscribed or duct carcinomas (2) The second point concerns the length of time that a tumor may exist before clinical diagnosis is possible A time lapse of forty-six months occurred in a woman with advanced mazoplasia cystica, which effectively prevented clinical recognition of a duct carcinoma A circumscribed carcinoma, C 1195, was still not palpable after more than twenty-one months Cancers have a much longer life than clinicians usually realize. Animal experiments translated into terms of human life span suggest that in man a carcinogenic agent takes ten years or more to produce a tumor of clinical size. The facts of animal experimentation are well known in theory, but their significance is often lost sight of when it comes to dealing with human cancers When all the data are taken into

consideration it must be conceded that few palpable tumors may be thought of as early.

So far our measurements have taken no account of secondary breast tumors In duct carcinomas, apart from possible transition to scirrhus, secondary foci do not greatly alter the prognosis. Tumors that produce metastases in lobules at a distance from the main growth are certainly more virulent, but since only one neoplasm of this type has been measured we have no statistical confirmation of this opinion.

The work has scarcely begun and some considerations are theoretical rather than practical. What is being measured is the over-all increase in volume of tumors 0.4 cm. in diameter or larger and not the rate of growth of any one part of the tumor. While it is necessary to be alert to possible sources of error, the x-ray film remains the only way of measuring the rate of growth of a tumor and of giving a reasonably accurate idea of its duration.

UNSUSPECTED CANCERS

Discovery of an unsuspected neoplasm is perhaps the most important contribution that mammary roentgenography has made to the patient's welfare. An unsuspected cancer is one which a practitioner of average ability is unable to diagnose. The word average is stressed because most women come under the care of their personal physician who cannot be expected to specialize in diseases of the breast. Top-flight surgeons are seldom wrong in their estimate of a tumor they can feel, but even they are not likely to discover an asymptomatic, nonpalpable neoplasm. In any case it is impossible to refer every woman to a breast surgeon of the first rank. Some ancillary means of diagnosis is necessary.

Broadly speaking, unrecognized cancers are either palpable tumors erroneously diagnosed benign, or nonpalpable, tumors. They fall into four groups:

1. A palpable tumor is diagnosed benign The surgeon feels a solitary movable mass or multiple masses which give the impres-

sion of cysts or fibroadenomas (figs 195, 196) A solitary, smooth, movable cancer is usually of the circumscribed variety Even roentgenographically it may be hard to distinguish from a cyst, unless part of the margin is irregular or a "tail" of fibers issues from the growth at one point (figs 182, 196) Age of the patient and clinical history should always be considered before making a diagnosis of cyst In cases of doubt recourse may be had to aspiration. Multiple discrete masses may turn out to be duct carcinoma (fig 186) On the film the diagnosis is very easy to make, but the clinical findings are so unlike those of carcinoma that an inexperienced surgeon may refuse to believe the roentgenogram.

2 Many unsuspected malignancies lurk in lumpy breasts with no dominant mass The nodules are usually bilateral, they are irregular and vary in size. Most often they are due to adenosis, sometimes to mazoplasia cystica arising on the basis of adenosis Occasionally fibroadenomas are present These women suffer from multiple surgical interventions Some of our patients had undergone as many as four operations before the carcinoma was discovered on the x-ray film. Figures 183 and 193 illustrate typical cases

3 Patients in the third group present no palpable mass Vague symptoms, expressed perhaps by a 'drawing feeling" or an ununusual type of pain may arouse suspicion in an experienced observer Symptoms, however slight, with no discoverable cause demand x-ray investigation (figs 197, 198, 200)

4. Some carcinomas are completely asymptomatic. No mass is felt and nothing draws attention to the disease. Asymptomatic women are unlikely to present themselves for examination, but in a recent survey of 1,300 volunteers, certified by their doctors to be free of any breast lesion requiring surgery, cancer was discovered in fifteen. Figures 192 and 199 illustrate two of these cases

An analysis of the distribution of the four groups in fifty-eight clinically unsuspected carcinomas showed an incidence of 52, 23, 17 and 8 per cent, respectively

Although occult cancers are not unsuspected and are therefore



FIG. 198 C 2396. Nonpalpable carcinoma Patient aged forty-two years Complained of premenstrual pain in the left nipple for six weeks She claimed that there was slight retraction, but this, although noted at the time of operation, could not be verified by the attending physician There was no palpable mass X-ray examination was requested as part of a check-up before the patient went abroad

The x-ray film shows a small spiculated tumor 1 cm in diameter just beneath the nipple A few minute calcified particles are seen in it. The nipple is slightly retracted. Drawing from x-ray film shows relation of tumor to nipple Pathologically the tumor was a duct carcinoma with transition to scirrhus

cases with symptoms Not sufficient time has elapsed for similar data to be available for the breast, but from what we know of tumors that were missed and picked up three or four years later, Rigler's conclusions are valid in principle for mammary cancers Even after the lapse of many months most of the preclinical tumors of our series had not metastasized to the axillary nodes



FIG 199 N 355 Unsuspected asymptomatic carcinoma. Age forty-one years Seen by physician three months before for premenstrual pain in both breasts Multiple soft masses palpated bilaterally X ray films show an area of increased density in the outer portion of the breast (arrow). Its margins are irregular and faintly spiculated. No calcification was visible Operation revealed a duct carcinoma.



A B

FIG 200. Linear nodular thickening in both upper outer quadrants masking carcinoma of the left breast Age forty-two years The patient presented herself with tender cordlike thickenings in both breasts near the axillae. Last menstrual period was seven years before following hysterectomy for myomas

A. X-ray films show the upper portions of both breasts near the axillae The right presents a spiculated mass a little over 1 cm in diameter, typical of scirrhus (arrows). An opacity, the cord-like swelling felt clinically, is seen below the tumor. The left breast presents a similar cordlike opacity.

B. Slicer section of tumor.

Table VIII is an analysis of 209 consecutive cases of carcinoma. Clinically, malignancy was either diagnosed or suspected in 151 cases, roentgenographically, 194 cases were so labeled. The diagnosis of "suspected malignancy" is here considered the equivalent of "carcinoma" Definitive diagnosis must be made by operation if necessary In practice the patient will be brought to treatment in the same way as a patient labeled "carcinoma," but with more hope of avoiding a mutilating operation In this series the radiologists diagnosis compares favorably with the surgeon's impression—194 cases correctly diagnosed by radiologists as against 151 by surgeons The surgeons, however, should not feel discouraged, since of 58 clinically unsuspected cases, 48 were diagnosed and brought to treatment on the basis of the x-ray film. Five cases recognized clinically were missed by the radiologist, 10 of the 209 were missed on the film and clinically The figures suggest that if surgeons and radiologists will combine their skills 95 per cent of cancers will be recognized and many early tumors will be uncovered while still in the operable stage.

Hitherto the detection of a mass in the breast has been left to the attending physician, the surgeon, or the patient herself In

TABLE VIII

Comparison of Roentgen and Clinical Diagnoses in 209 Consecutive Cases of Breast Cancer

Diagnosis	Correct	Error
Clinical exam.	151 carcinomas diagnosed or suspected, 72%	58 called benign, 28%
X ray exam.	194 carcinomas diagnosed or suspected, 93%	15 called benign, 7%
Combined x ray and clinical exam.	199 carcinomas diagnosed or suspected, 95%	10 called benign 5%

spite of intensive propaganda and insistence on early diagnosis and treatment, no real improvement in mortality statistics has been accomplished. The average diameter of the tumor when first seen is still 3.5 cm. Even when a mass is found the differential diagnosis is so uncertain that surgeons advocate resection of any dominant lump and leave it to the pathologist to decide on its nature. One unfortunate by-product of this plan of treatment is the blunting of the surgeon's clinical sense. Meticulous attention to history and symptomatology is needed to alert the diagnostician to the possibility that he is dealing with a small carcinoma If operation is to be performed anyhow, a certain carelessness is likely to develop. A young resident voiced this attitude when he refused at first to interest himself in an exhibit of diagnostic x-ray films of the breast, saying, "What's the use, a lump must be operated on anyhow." Fortunately the demonstration of cases where operation was not indicated and of tumors which could not be discovered except by x-ray examination induced him to change his mind.

The fact must be faced that once a tumor becomes palpable the chances of cure are seriously diminished. Even nonpalpable growths are not always early, witness the sentinel nodes of occult cancers. We insist that a palpable tumor is a late tumor. The chief hope of cure at the present time lies in early diagnosis and in the present state of our knowledge early diagnosis is only possible by means of the x-ray film Mammary roentgenography should be taken up by health clinics as a routine measure along with chest examinations. By so doing not only will many more true early cancers be discovered, but with increasing experience, precancerous states—especially intraductal hyperplasia—will be recognized. Although many lesions of this type have already been uncovered, we believe that as is inevitable in the present state of our knowledge, an equal number have probably remained undetected. Further experience along this line will be sought, for with the removal of every precancerous lesion a mutilating operation if not a life has been saved.

This is not to say that every tumor can be diagnosed roent-

genographically In the previous section some account was given of cases that were missed But it must be remembered that months or years may pass before a preclinical tumor gets to the stage of being recognizable on physical examination The radiologist may miss the chance for cure. The only consolation is that at the time when he tackled the problem no one else could have made the diagnosis

THE SCIENCE OF COMPARATIVE PATHOLOGY AND RADIOLOGY

Our studies were originally directed to perfecting roentgenographic diagnosis of breast lesions The method used involved comparison of films with the actual tissue cut into slices and stained with hematoxylin (Appendix III) The tissue was cut as far as possible in the axis represented on the most characteristic film. The over-all view given by slicer sections is especially valuable for demonstrating normal and abnormal architecture in the breast. Long familiarity with lesions shown by this method made diagnosis easy, and once the lesions were recognized in the section they were not difficult to pick out in the sometimes confused medley seen on the x-ray film. The x-ray film gives a tridimensional picture compressed into two dimensions The slicer gives only a two-dimensional view One section does not show all the structures represented on the film, but when serial sections are made it is possible to get a composite visual impression of the entire breast If patterns appear which the pathologist does not recognize, further study must be undertaken until the unidentified shadows are matched with the structures they represent.

As would be expected, ability to see and recognize the enormous variety of shadows displayed on the x-ray film was not acquired in a day Eight years of constant study and practice have gone into the making of such results as we have now achieved In early days a good view of a palpable cancer was considered worthy of praise. Now we are striving to perfect our methods for uncovering non-palpable cancers and precancerous states And the end is not in sight.

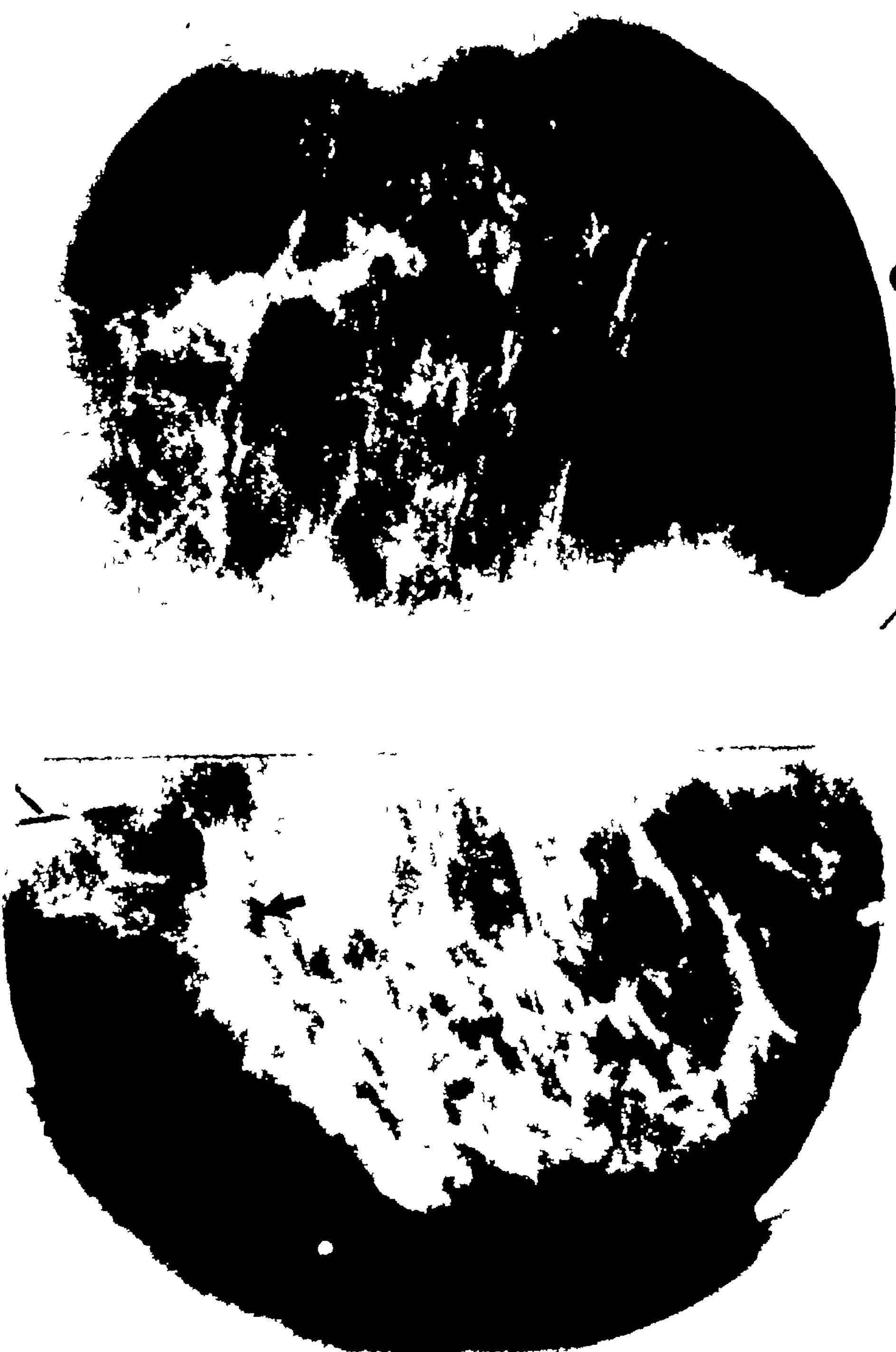


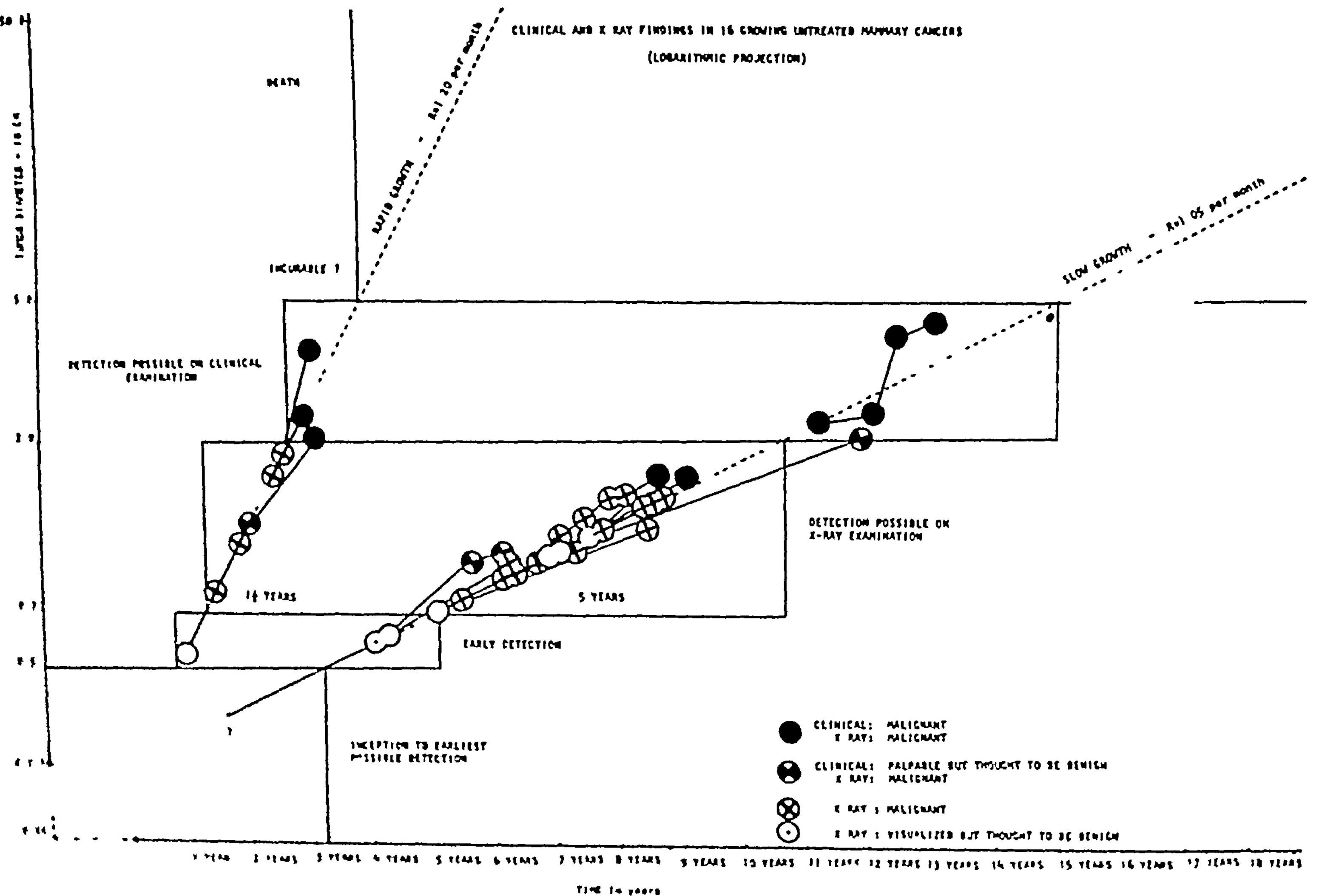
Fig. 201.

The application of comparative radiology and pathology to roentgenographic diagnosis is only one side of the story The reverse procedure, the review of pathology in the light of the x-ray film is equally important. Most pathologists must perforce be content with the very limited view of a mammary disorder afforded by histologic sections While microscopic preparations are ofttimes the only means of identifying a specific lesion they are insufficient for study of nosologic entities Moreover, it is not possible to observe changes in tissues by excision of the part concerned. The natural history of diseases is thereby lost to us Ideally every opacity seen on the film should be capable of interpretation by the pathologist. Two factors interfere with the realization of this ideal The first is the overlapping of structures on the three-dimensional film. The second is the difficulty of bringing objects at different levels into the same focal plane. On any x-ray exposure with a short film-target distance, tissues not close to the film are out of focus Hence in a lateral view structures in the median part of the breast are slightly blurred. In the A.P or cephalocaudad view elements in the upper part of the breast are farthest from the film and may not stand out distinctly For instance, the spicules of a scirrhous carcinoma might not be visualized and unless a second film is taken at a different angle the radiologist might be misled. It is rather common for cysts, clearly visible in one view, to disappear completely in films taken from another angle. For this reason two pictures in different positions are always made. Technics should vary whenever necessary in order to get the lesion as close to the film as possible.

The two processes of identification on the film of structures

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FIG 201 C 375 Scirrhous carcinoma of right breast fibrosis in corresponding area of left breast. Age sixty-seven years. The x-ray film of the right breast (A), shows a spiculated mass in the upper outer quadrant (arrow). An elongated opacity, pathologically consisting of ducts filled with carcinoma cells, extends toward the nipple. The left breast (B), presents a fibrous patch corresponding in location to the tumor


CLINICAL AND X RAY FINDINGS IN 16 GROWING UNTREATED MAMMARY CANCERS
(LOGARITHMIC PROJECTION)
DEATH
INCURABLE ?
RAPID GROWTH - Rel 20 per month
SLOW GROWTH - Rel 05 per month
DETECTION POSSIBLE ON CLINICAL EXAMINATION
DETECTION POSSIBLE ON X-RAY EXAMINATION
1½ YEARS
5 YEARS
EARLY DETECTION
INCEPTION TO EARLIEST POSSIBLE DETECTION
CLINICAL: MALIGNANT
X RAY: MALIGNANT
CLINICAL: PALPABLE BUT THOUGHT TO BE BENIGN
X RAY: MALIGNANT
X RAY : MALIGNANT
X RAY : VISUALIZED BUT THOUGHT TO BE BENIGN
TIME in years

familiar to the pathologist and identification in sections of previously unobserved processes are closely intertwined. Indeed, so close is the connection that the two elements are hard to disentangle. For example, adenosis was first called to our attention by the fact that numbers of cases of so-called "cystic disease" were sent to us in which no cysts appeared on the x-ray film. We followed the cases to the operating room. No cysts were present in the excised tissue. The films were restudied. Characteristic opacities were found which followed the arrangement of corresponding groups of hypertrophied lobules visualized in slicer sections of tissue from the cases operated on. The problem of the nature of the cystlike structures felt clinically might have been solved either way. Actually it was the pattern of opacity on the film which furnished the first clue to the nature of the lesion and gave impetus to our study of adenosis.

Secretory disease is a good example of the way in which roentgenography brought together scattered observations extending over many years and wove them into a coherent whole. Different facets of the disorder were long known as "comedo mastitis," "varicocele tumor," "periductal mastitis," and "mammary duct ectasia." In 1939 we called attention to the connection with plasma cell mastitis. But not until the various phases of secretory disease were reflected on the x-ray film was it possible to correlate the pseudolactation which could start deep in the breast, with dilated ducts, fibrosis, and finally calcification. The connection with plasma cell mastitis was confirmed and further studies revealed the link between plasma cell mastitis and intramammary abscess.

Anatomic studies in normal women are possible only by means of the x-ray film. Observations on the changes in lactiferous ducts

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FIG. 202. Logarithmic projection of volume increases in sixteen untreated mammary cancers. Tumor volumes of sixteen growing mammary cancers have been plotted logarithmically. Solid lines indicate successive examinations of the same case (*cf.* table VII).

during the let-down in nursing mothers could have been made in no other way. But had it not been for a thorough background knowledge of breast anatomy the significance of what we saw might well have escaped us.

Pathologists have been stirred to a better appreciation of types of calcification and of their significance in breast disease by the discoveries of radiologists. Calcification in benign conditions is chiefly of importance as indicating an obsolescent lesion which does not need operation The typical minute punctate calcifications of malignant disease may signify intraductal carcinoma in situ, but are much more likely to stem from a frankly malignant lesion The pattern of calcification may be pathognomonic for duct cancer and if no tumor margin is seen an uncomplicated or "pure" duct tumor may be postulated The chances for cure are excellent. If the tumor begins to show spiculated margins it is probably of the mixed duct-scirrhus variety and prognosis is less happy. Although the x-ray film is usually the better guide, the pathologist should study the histologic site and character of calcification along with other features of the tumor. A better insight into the degree of malignancy of a particular growth may be gained thereby.

Perhaps the most important outcome of the combined method of approach is the classification of certain common types of carcinoma and their correlation with the type of breast in which they grow, their rate of growth, and their prognosis We have always been aware of the wide margin of variability in normal breasts, but the existence of distinctive patterns of mammary tissue which admitted of classification was not discovered until some 700 x-ray films had been scrutinized in an effort to determine the kind of breast which might predispose to malignant disease Once seen on the x-ray film, breast types could be identified in slicer sections with comparative ease, but due to the small area under scrutiny they were not diagnosable by ordinary histologic methods. When it was shown that scirrhous tumors occurred chiefly in normal types of breast and the much less malignant circumscribed and duct carcinomas in breasts with dysplasia, and

when evidence was obtained that growth in the two last-named tumors proceeded at a much slower rate than in scirrhus, histologic study could come into its own Anatomically, hyperplasia of the myoepithelium could be invoked as the principal barrier retarding passage of the tumor from duct lumen to surrounding structures The curious drop in mortality after the five-year period is thereby explained A palpable scirrhus is usually fatal within five years At the other end of the scale are the duct carcinomas which, if they remain true to type, may last twenty years or more. Circumscribed tumors are intermediate in their effect, our experience suggests that their average duration is around seven to ten years These studies are still in their infancy Much work is needed before the results can become definitive. Meanwhile enough has been done to establish the value of a new approach to the problems involved.

Original investigations by new methods involving so extensive a subject as the human breast cannot in the nature of things be complete. Our observations may be compared to a scaffold. The building is far from finished. The reader will find many loose ends and much to criticize. In any research there is ebb and flow of contradiction and confirmation It is precisely to encourage the testing of our conclusions and with the hope that others will add to the superstructure that this volume is published.

Appendices

APPENDIX I

VOLUME CHANGES IN MAMMARY DYSPLASIA

Figure I Volume changes in a case of fibroadenoma.

The fibroadenoma occurred in a volunteer aged twenty-one years, who came regularly for measurements The right breast showed a normal cycle, the left contained a fibroadenoma about 2 cm. in diameter in the upper outer quadrant and, except for one premenstrual measurement, was a little larger than the right breast The chief difference in the graphs is that the left breast shows a postmenstrual rise rather than a fall after the 29 days cycle. Fibroadenomas containing active mammary parenchyma undergo cyclic changes, but growth and regression lag behind the rest of the breast. It is possible that delayed cyclic enlargement of the tumor rather more than compensated for regression in the rest of the breast.

Figure II. Volume determinations in two cases of mammary hypertrophy

A. A girl of sixteen years with right unilateral hypertrophy showed quite different graphs in the two breasts At the time the measurements were made the patient was undergoing a course of x ray treatments to the pituitary The hypertrophied breast diminished in size, the contra lateral breast showed no change.

B. Aged twenty two years, this girl had hypertrophy of both breasts with premenstrual pain for two years The graph shows no correlation between the breast volume and the menstrual cycle.

Figure III. Severe dysplasia associated with distant bacterial foci.

M. F and J A. Vartine (1947) noted that foci of infection maybe associated with pain in the breast and that these patients do not respond to pituitary irradiation The following case of mazoplasia cystica with secretory disease and plasma cell mastitis responded poorly to pituitary irradiation, but improved dramatically after removal of abscessed teeth. Severe premenstrual pain and swelling had been present for two years

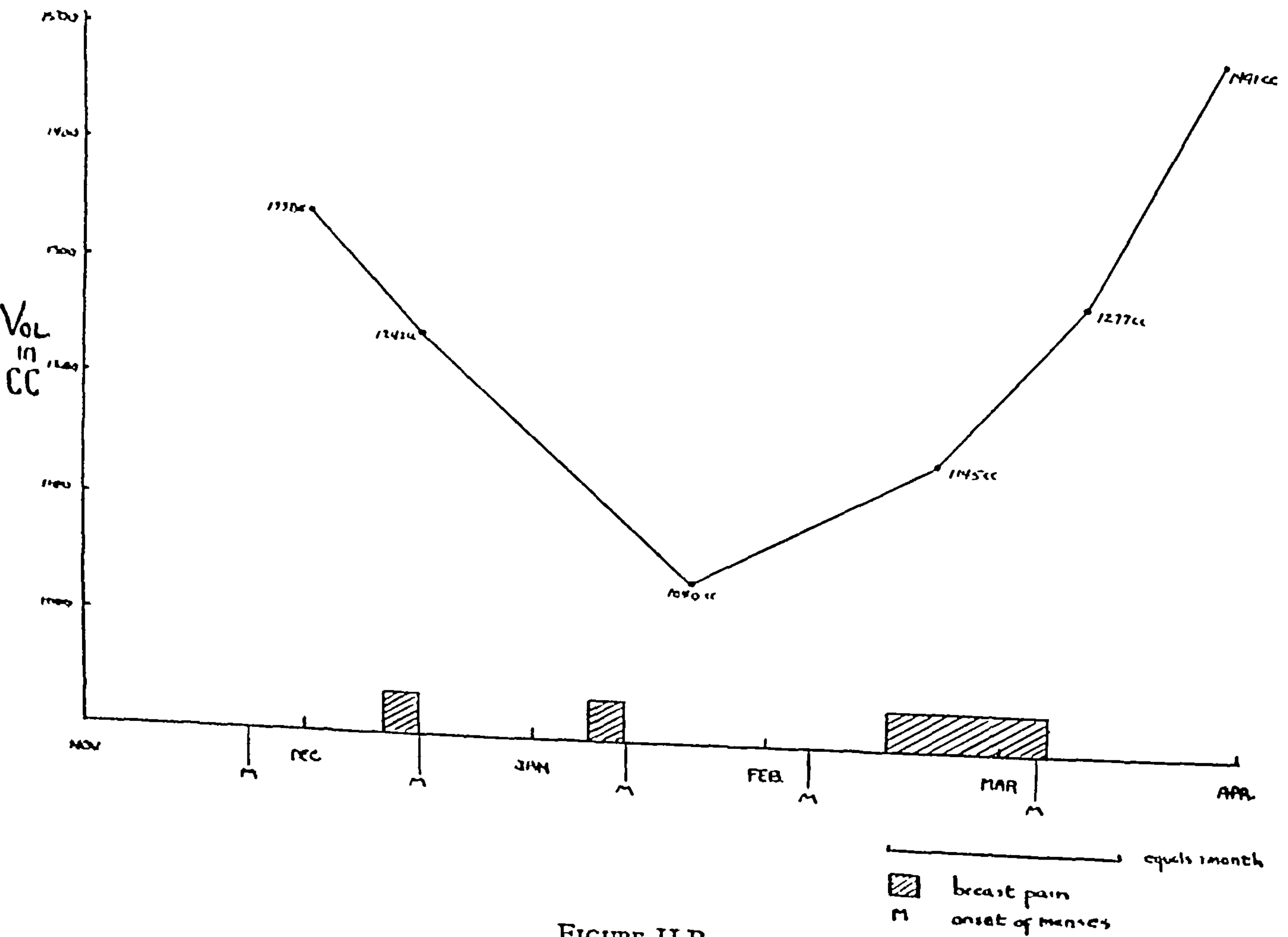

VOL in CC
1277cc
NOV
DEC
JAN
FEB
MAR
APR
M
equals 1 month
breast pain
M onset of menses

FIGURE II B.

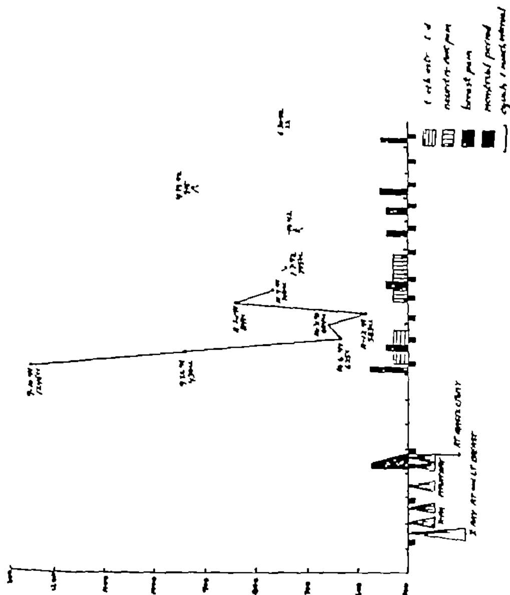


FIGURE III

Simple mastectomy was performed on an enormously swollen and livid right breast. Pathological examination disclosed advanced mazoplasia cystica, secretory disease and plasma cell mastitis. Bacteriological examination was negative. Volumetric measurements of the left breast were made three months later when similar symptoms of intense premenstrual swelling pain, and lividity were present. It could be presumed that the pathology would be similar in the two breasts The breast

volume on the first day of the menstrual period was 1245 cc³. Abscessed teeth were then discovered and when these were removed the breast volume dropped sharply Just before the onset of the next menstrual period it was 635 cc³. Relapses occurred due apparently to activation of bacterial foci, but pain and swelling were much less and gradually ceased

APPENDIX II

ROENTGENOGRAPHY OF THE BREAST—TECHNIC

Roentgenography is preceded by a clinical examination A marker may then be placed at the site of a dominant mass or wherever a lesion is suspected In this way the radiologist's eye is directed to important fields, and, when occasion warrants, fresh examination may be made of the suspected area Marking of scars is also advisable.

The x-ray examination comprises lateral, cephalocaudad, and spot film projections of both breasts The lateral views of the breast are taken with the patient lying on her side and the breast supported on wooden blocks or sand bags in order to obtain a true lateral profile. The tangential cephalocaudad views are taken with the patient standing erect with the breast supported on a platform which can be raised or lowered. In both views, care is taken to include the entire breast from the pectoral line to the nipple This is especially important in cases where a tumor lies close to the chest wall. The spot films may be made at any angle so as to bring the area under study as close to the film as possible. From the lateral and cephalocaudad views which are at right angles to each other, it is possible to localize a tumor and plot it on diagrams for surgical approach

Nonscreen film is essential A semicircular cone is used and the flat side is shaped so that it can be placed against the chest wall Smaller circular cones are suitable for the spot film projections Compression of the breasts is achieved with the cones The factors commonly employed by us are 25–35 KV, 1–3 seconds, 100 MA, and 14 inches film-target distance The focal spot is 0 3 mm Exposure time does not depend on the size of the breast, but on its density, therefore, longer exposures are used for dense young breasts while shorter exposures will be found adequate for large fatty breasts. A breast containing a large tumor as in advanced carcinoma requires longer exposure time than its normal

counterpart. A technic chart based on breast densities and film target distance can be devised for the benefit of inexperienced technicians

Meticulous attention to technic is necessary if utmost detail on the film is to be obtained, and without rigid care to technical factors, comparative periodic studies are not possible. Our films are *routinely slightly overexposed* for the purpose of revealing minute calcifications and the structures in the thicker portions of the breast. Bright spotlights are used for viewing the films

APPENDIX III

SLICER METHOD FOR THE PREPARATION OF LARGE BREAST SECTIONS

Apparatus required

Commercial Meat Slicer
Domestic Refrigerator

Method

Fix in 4 per cent formaldehyde for as long as necessary depending on the size of specimen. Very large specimens may be cut into thick parallel slabs and fixed against a flat surface. The specimen is frozen in the freezer compartment of an ordinary refrigerator Care must be taken to solidify the tissue without overfreezing The specimen should be wrapped in a moist cloth to prevent drying

The frozen specimen is cut with an ordinary meat slicer The thickness of sections can be varied from about 1 mm upward. In practice the thicker sections are sometimes desirable since they are viewed tridimensionally If a complete series is desired, numbered shellacked tags are prepared and each section separately labeled using a fine needle and thread.

Sections are stained in hemotoxylin, diluted 1 in 10 if the sections are to be stained overnight. A 1 in 20 dilution may be used if it is desired to stain for two days

The sections are washed rapidly and transferred to acid alcohol until differentiated. They are thoroughly washed and transferred to water to which a small amount of ammonia has been added. As soon as satisfactory bluing has been achieved the sections should be washed in running water If this is not done pinkish discoloration is apt to ensue.

The following steps are taken for dehydration and clearing:

70 per cent alcohol (four hours or longer); 95 per cent alcohol (two hours); Acetone (two changes, two hours in each); Xylol (two changes, two hours in each)

Sections are stored in mineral oil. All traces of xylol must be removed before permanent storing.

Mineral oil interferes to some extent with clearing, but the sections can be cleared again in oil of wintergreen. A 1 per cent solution of α-bromnaphthalene in mineral oil may also be used for clearing.

Sections are viewed with a dissecting microscope. The method is admirable for study of mammary gland architecture, but is not suitable for cellular pathology.

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